

Organic Chemistry IV

Organometallic Chemistry for Organic Synthesis

Prof. Paul Knochel

LMU

2014

OCIV

Prüfung:

Freitag 11. Juli 2014

9-11 Uhr

Baeyer HS

Wiederholungsklausur:

Donnerstag 11. September 2014

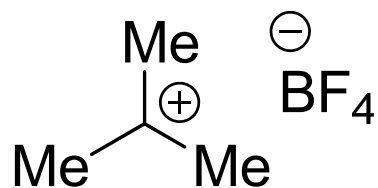
12-14 Uhr

Baeyer HS

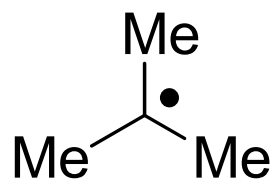
Recommended Literature

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

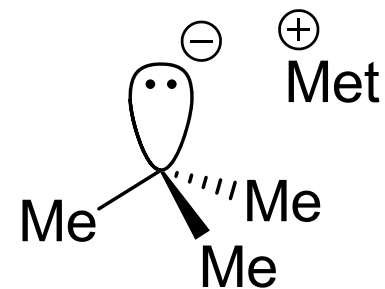
Importance of organometallics



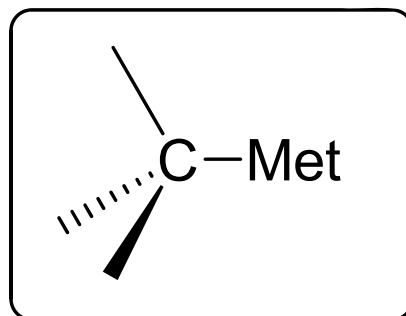
carbenium ion



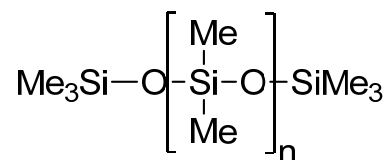
radical



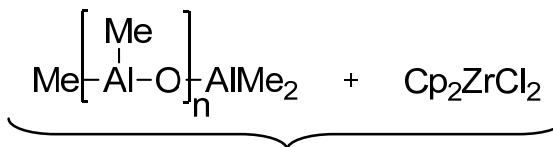
organometallic reagent



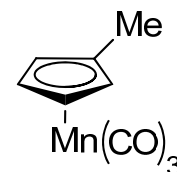
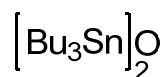
Industrial production



Silicone



Kaminsky catalyst
n=5-20 syndiotacticity of polypropylene

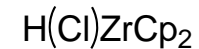
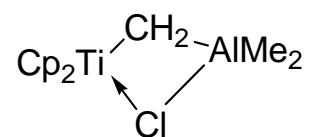
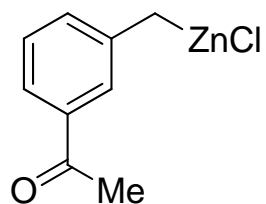
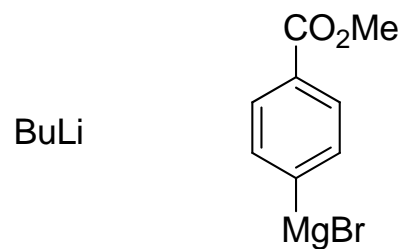


Industrial annual production of various organometallics

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

Organometallic reagents and catalysts for the organic synthesis

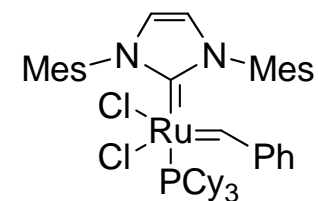
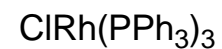
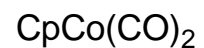
organometallic reagents:



Tebbe reagent

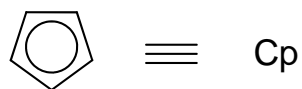
Schwarz reagent

organometallic catalysts:



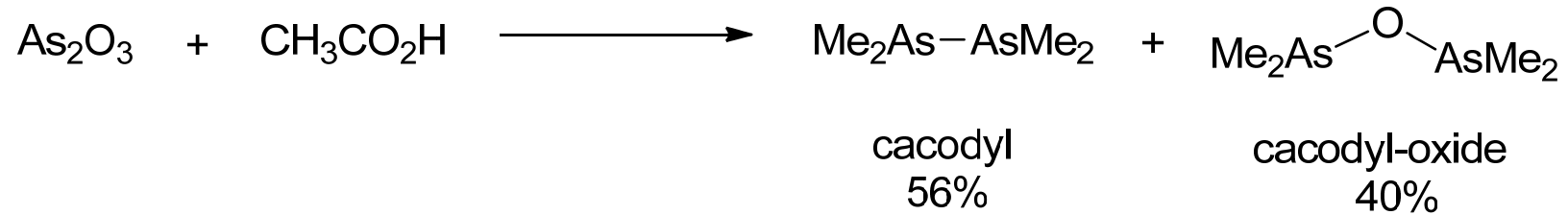
Wilkinson's catalyst

Grubbs II catalyst

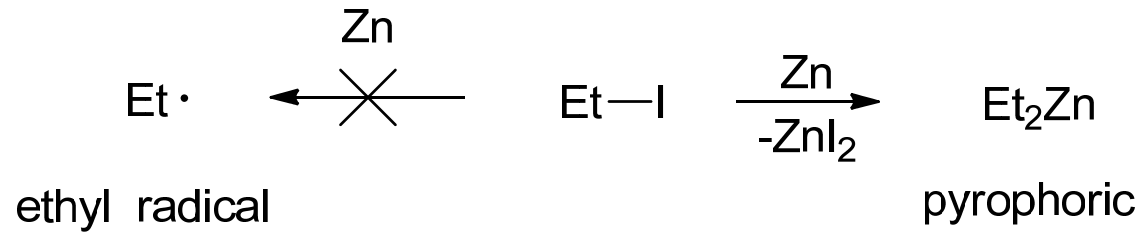


Historic point of view

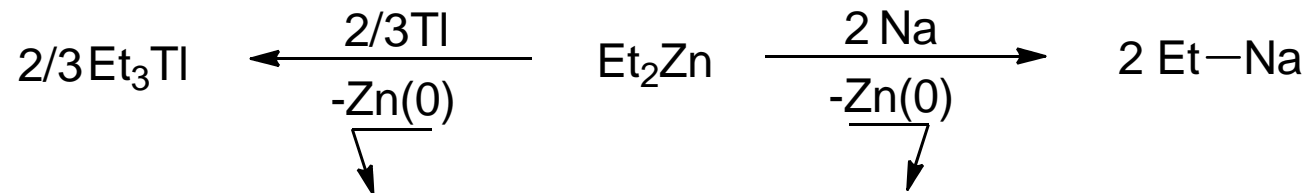
1757 - Louis Cadet de Gassicourt (parisian apothecary)



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

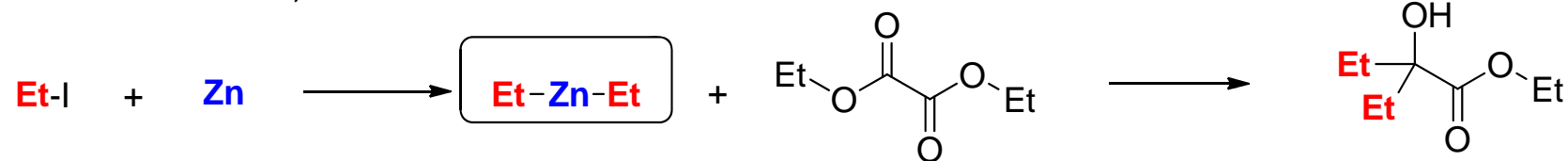


Universität Marburg (1848)

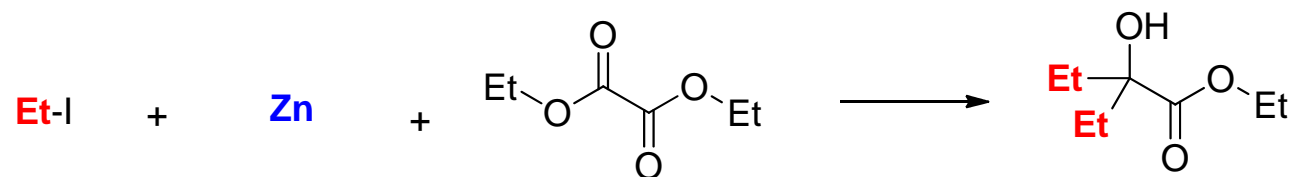


Organometallic chemistry of the XIX century

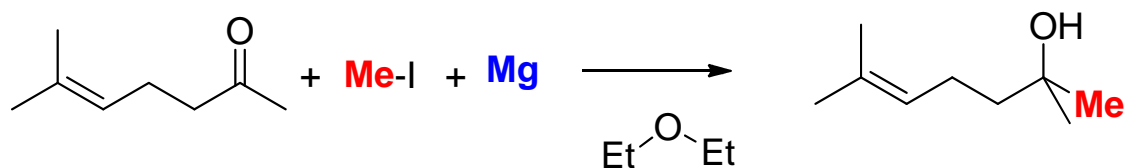
Frankland 1848, 1863



Beilstein 1862, Saytzeff 1870, Wagner 1875



Barbier 1899

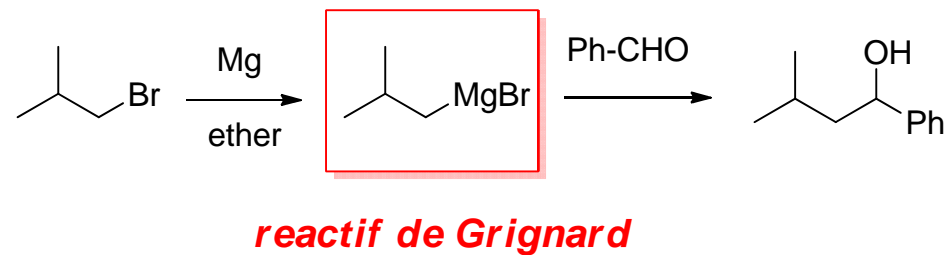
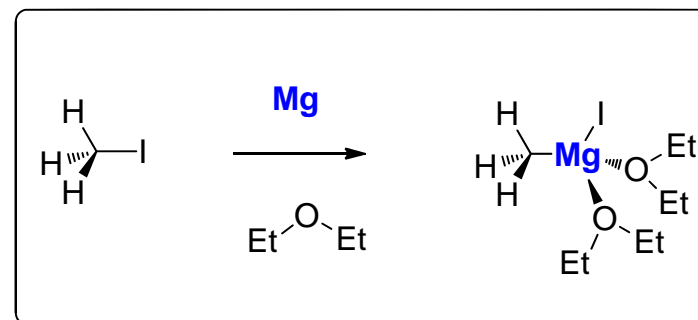


Ph. Barbier *Comptes Rendus de l'Académie des Sciences*, 1899, 128, 110

Organometallic chemistry of the XIX century



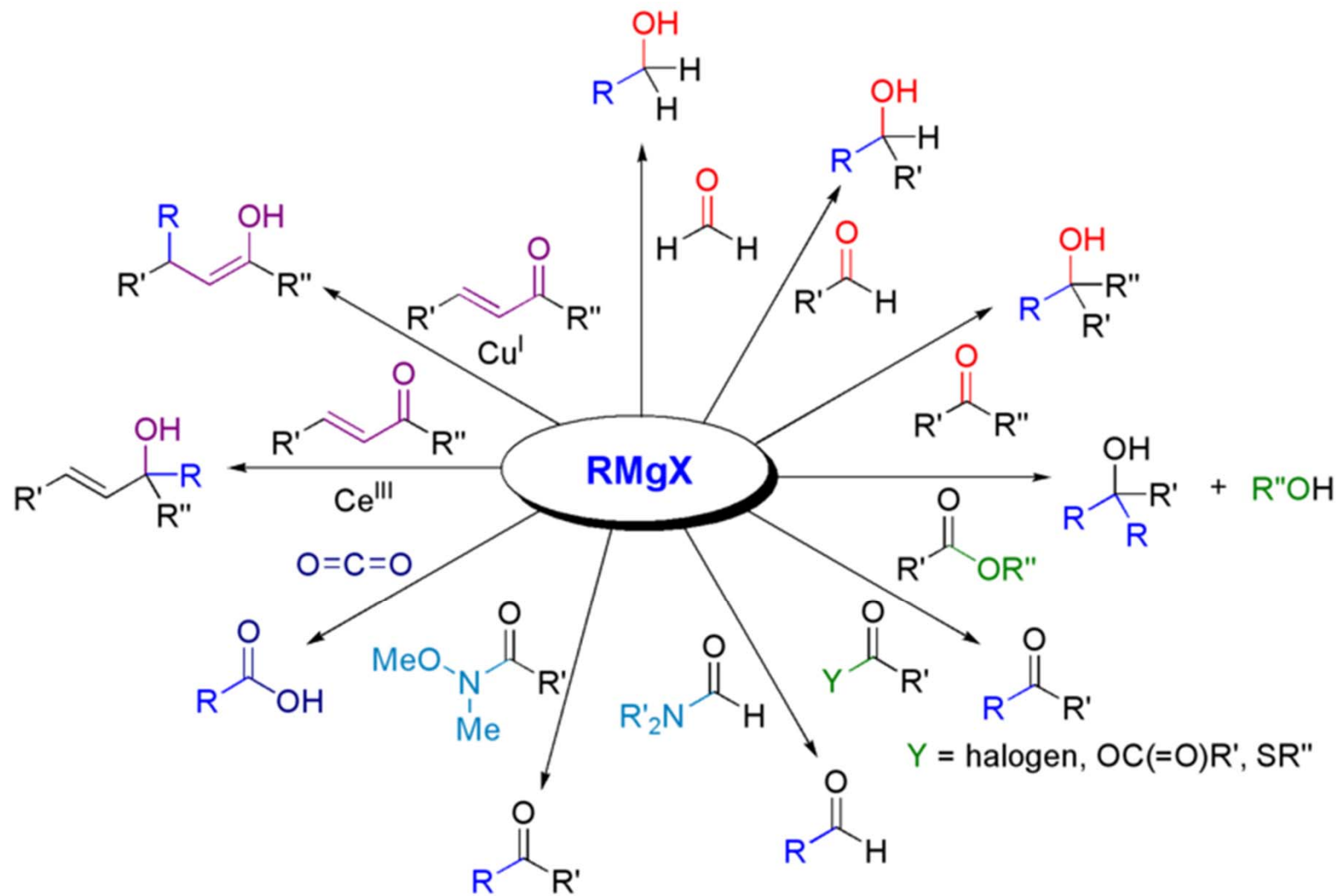
Pl. X. Victor Grignard dans son laboratoire de Nancy
1912



V. Grignard

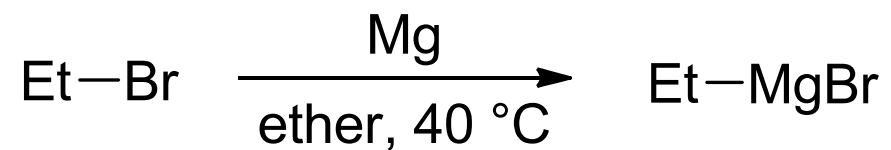
Comptes Rendus de l'Académie des Sciences, 1900, 130, 1322

Reactivity of the Grignard reagents



Historic point of view

Victor Grignard (1900)

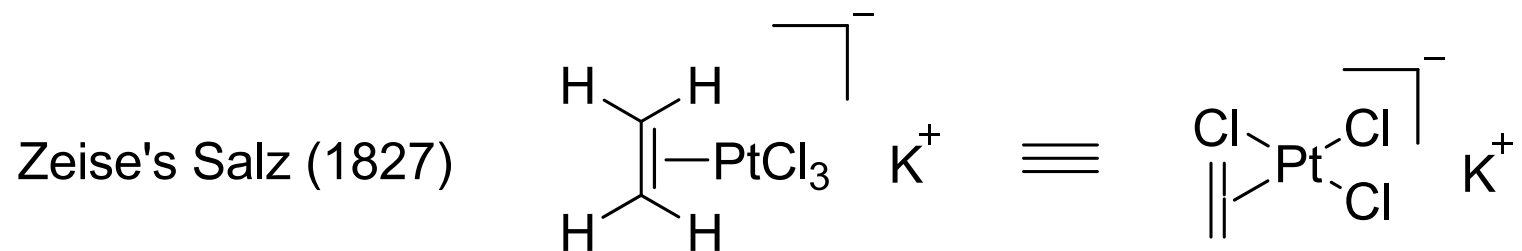


Karl Ziegler (1919)

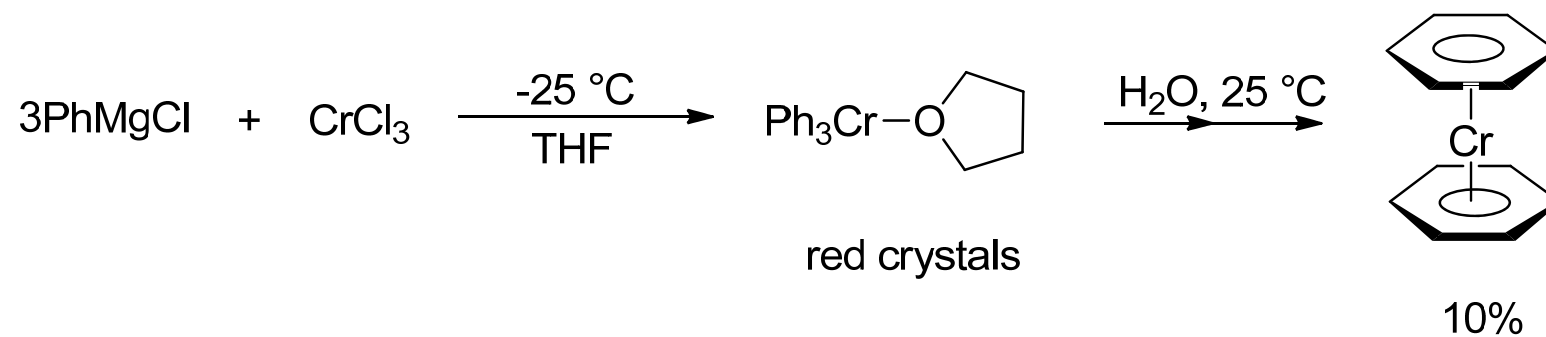


Historic point of view

first transition metal organometallics:



Hein (1919)

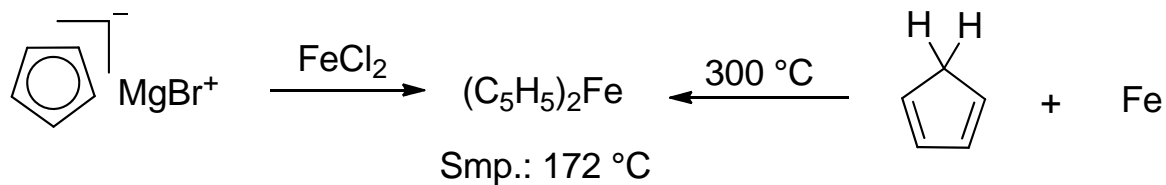


Historic point of view

1951 : synthesis of ferrocene

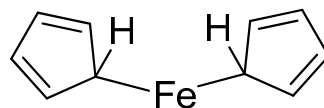
Pauson (Scotland) 7. August 1951

Miller 11. June 1951

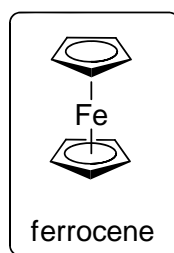


1952

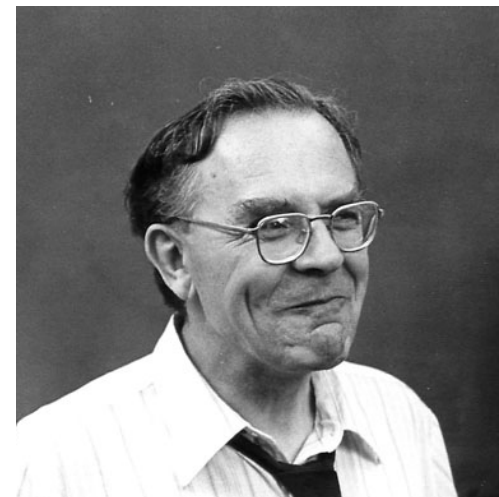
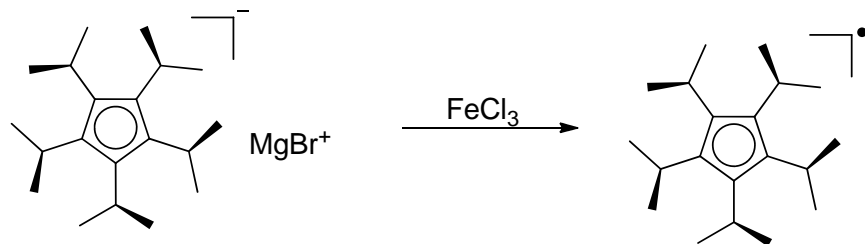
structural proposal by Pauson



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



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



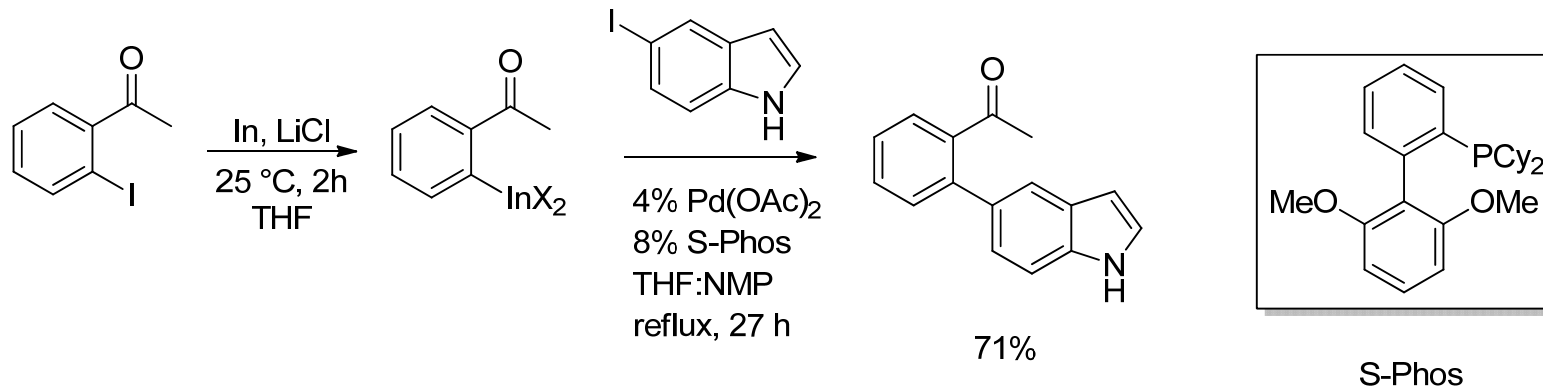
G. Wilkinson



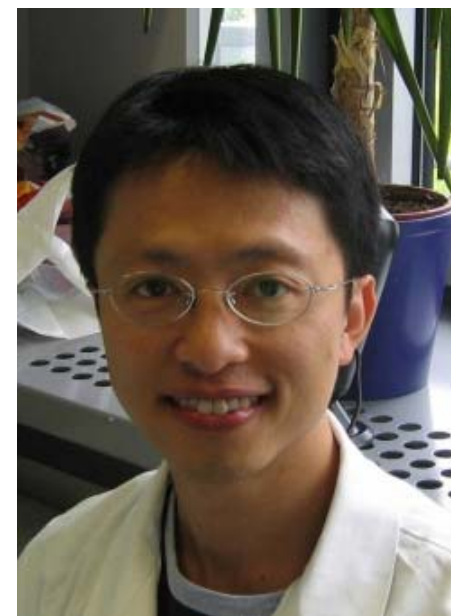
R. B. Woodward

Goal of the lecture

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



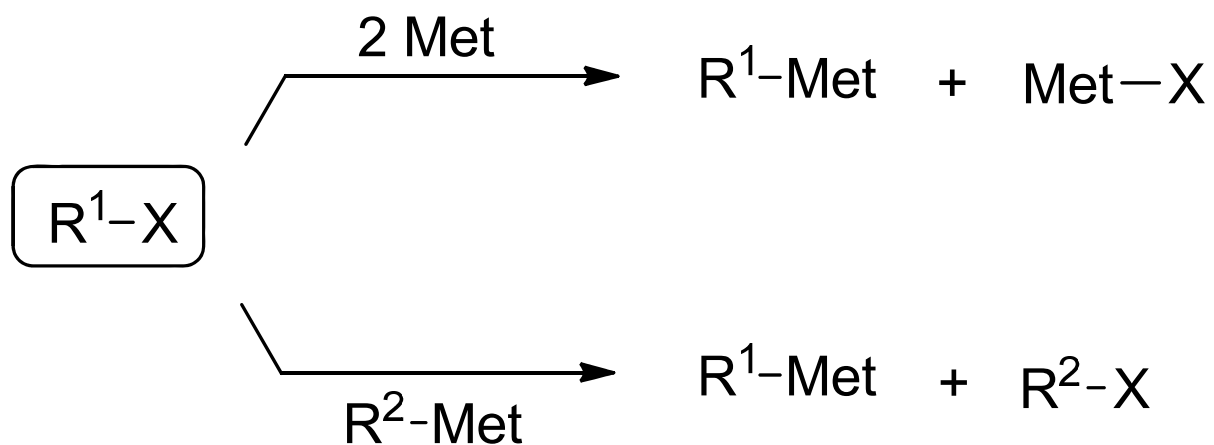
Y.-H. Chen, *Angew. Chem. Int. Ed.* **2008**, 47, 7648.



General synthetic methods for preparing organometallic reagents

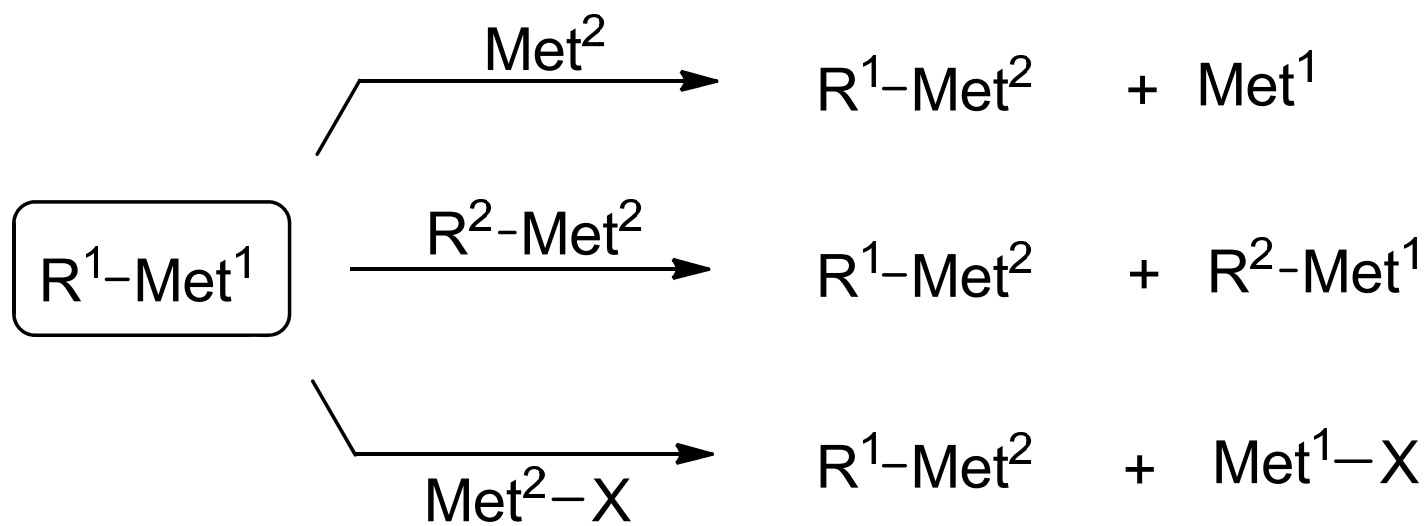
classification according to starting materials

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



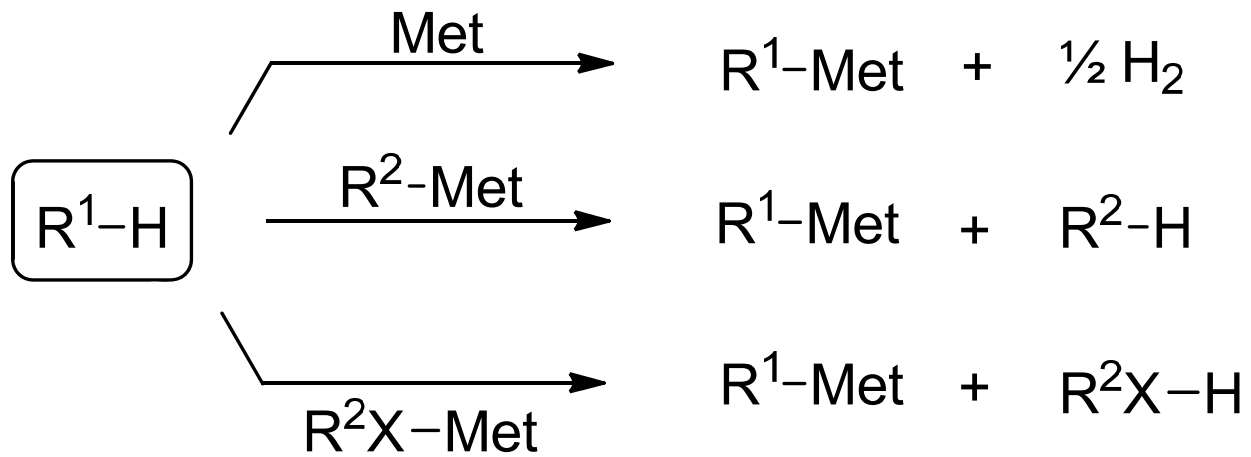
Classification according to starting materials

transmetalation



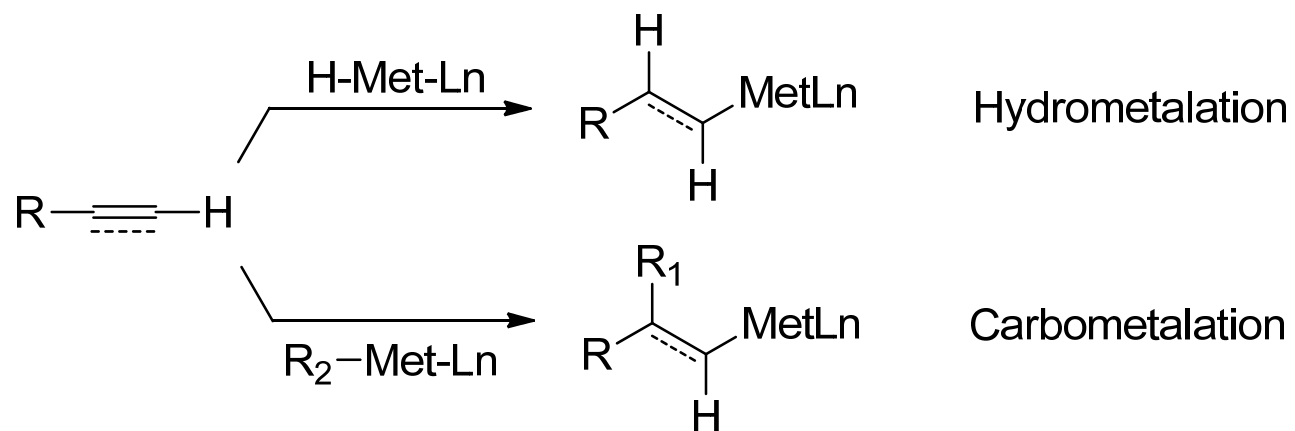
Classification according to starting materials

metalation



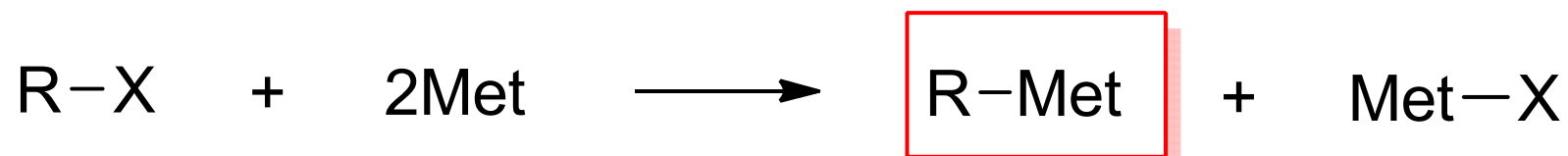
Classification according to starting materials

carbometalation and hydrometalation



Synthesis starting from organic halides

direct synthesis - oxidative addition



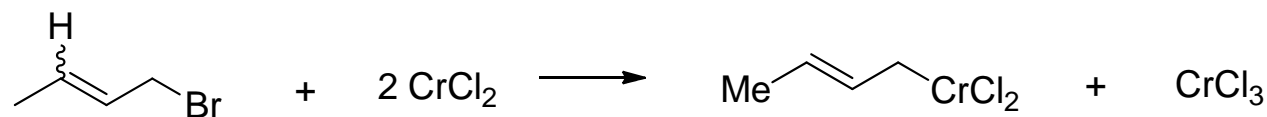
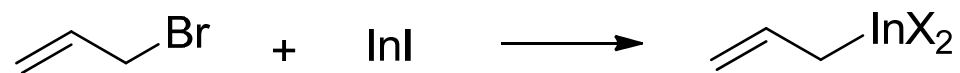
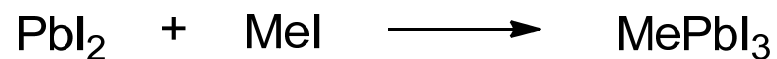
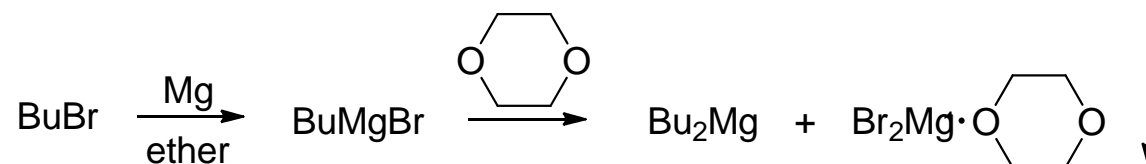
driving force of the reaction:

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



Direct Synthesis - Oxidative Addition

examples:

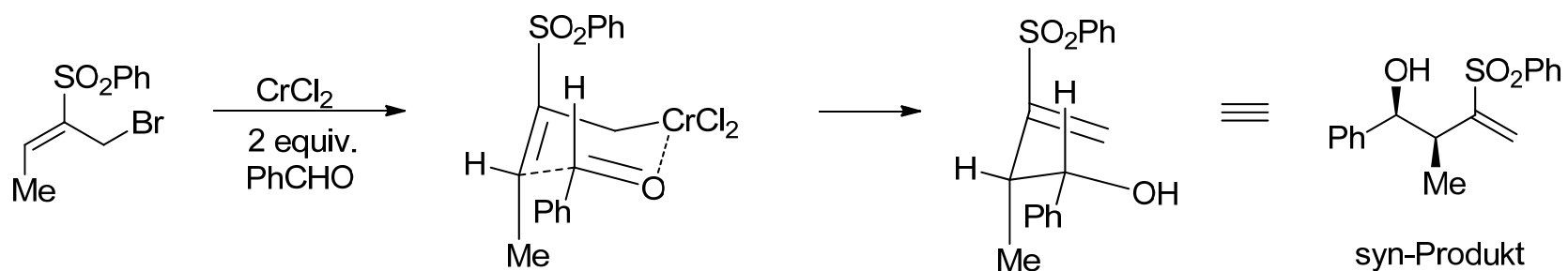
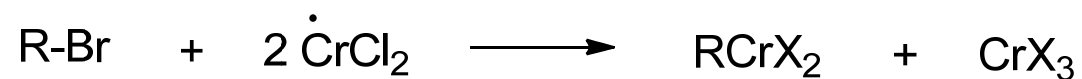
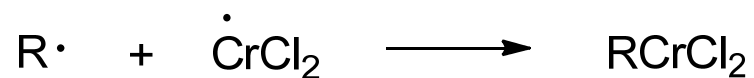
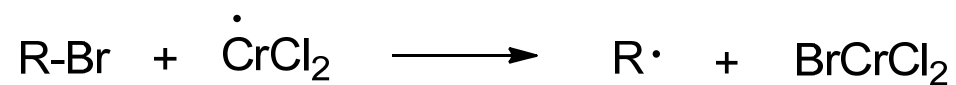


E/Z-mixture

pure E-isomer

Direct Synthesis - Oxidative Addition

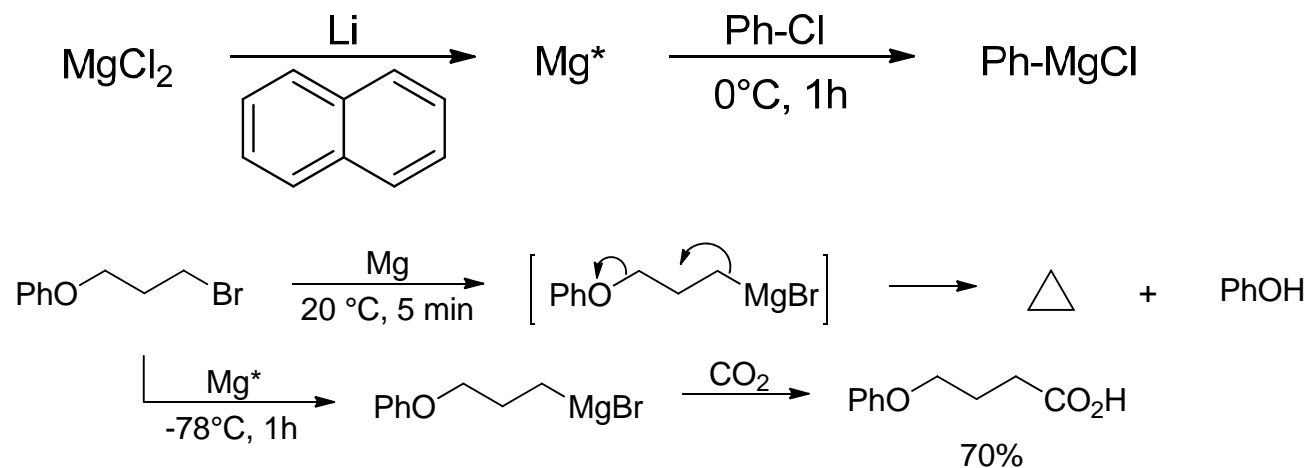
mechanism:



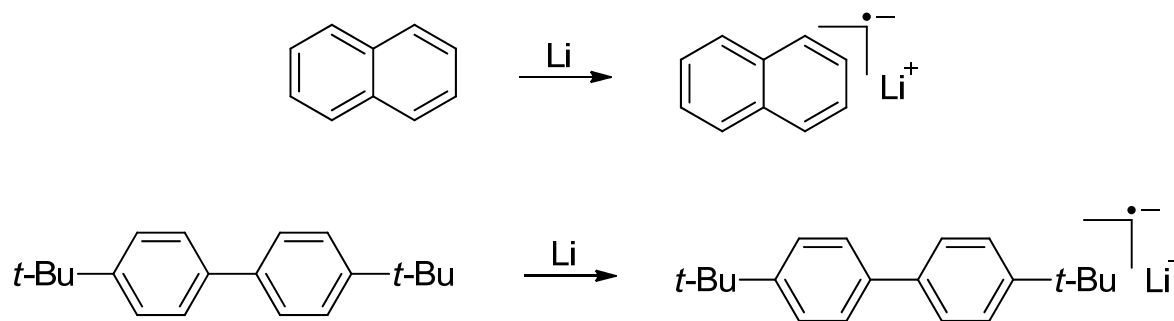
P. Knochel *Tetrahedron Lett.* **1986**, 27, 5091

Activation of the metal: the *Rieke*-approach

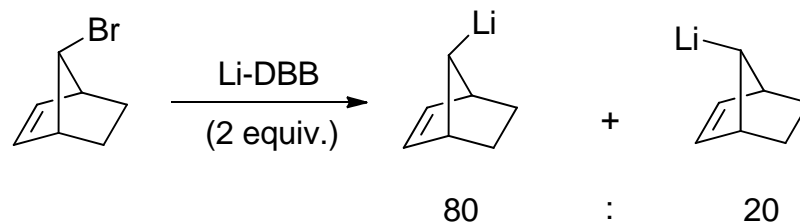
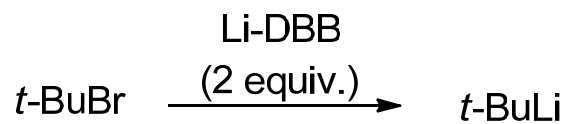
activation of the metal: R. D. Rieke, *Science* **1989**, 246, 1260



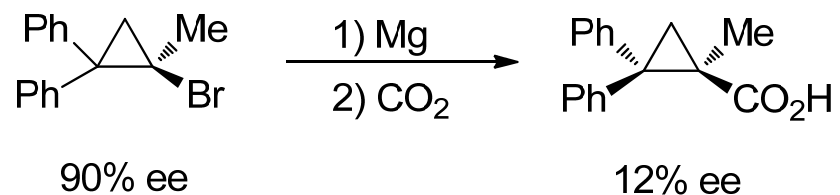
Activation of lithium: formation of soluble Li-sources:



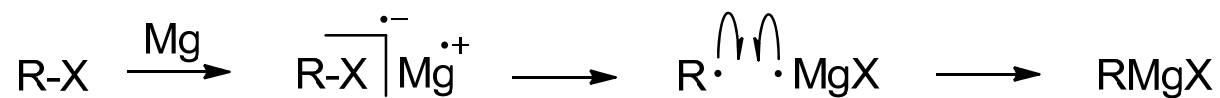
Mechanism of the metal insertion



loss stereochemical information

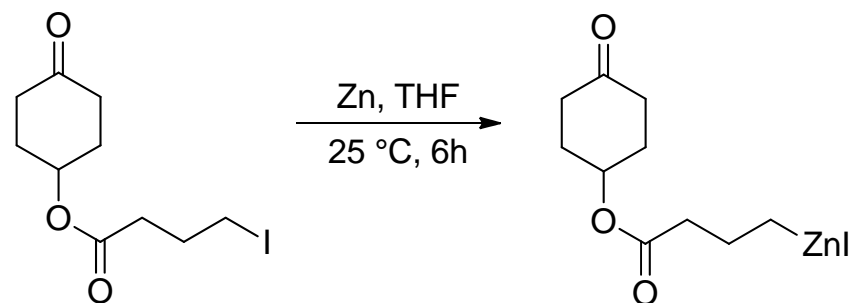
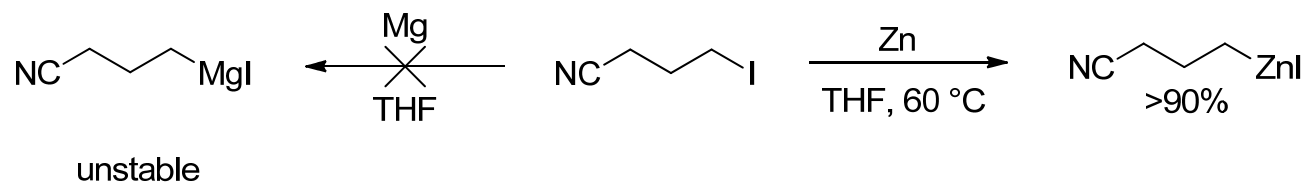


H.M. Walborsky: *J. Am. Chem. Soc.* **1989**, 11, 1896



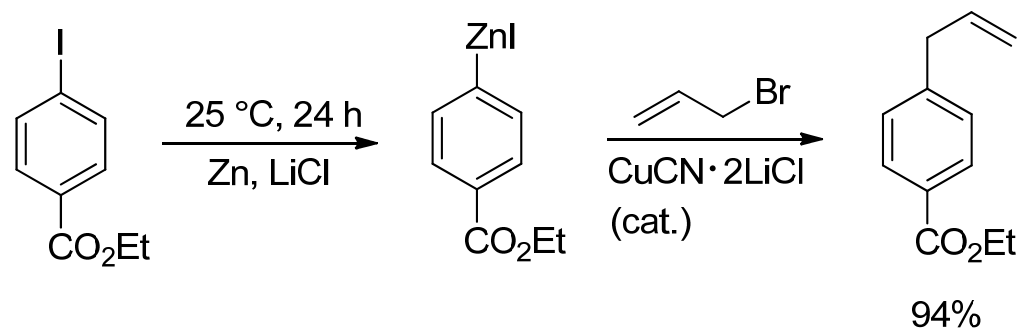
radical mechanism

Preparation of functionalized organometallics



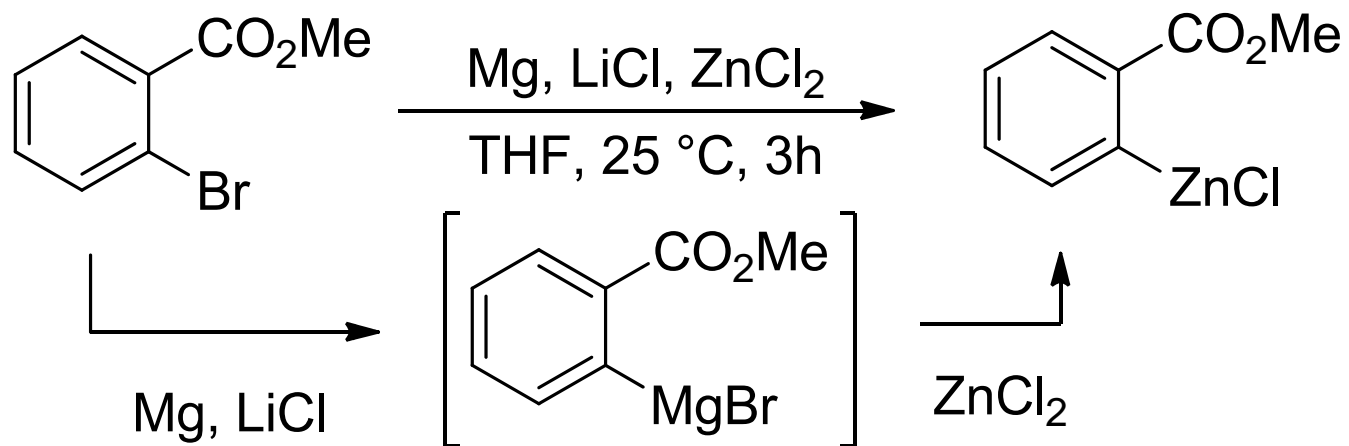
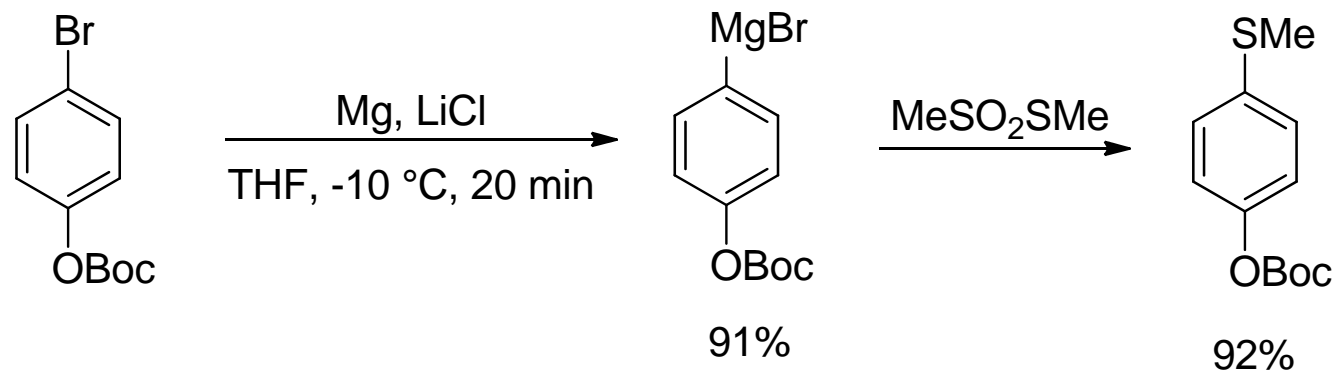
P. Knochel, *J. Org. Chem.* **1988**, 53, 2390

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



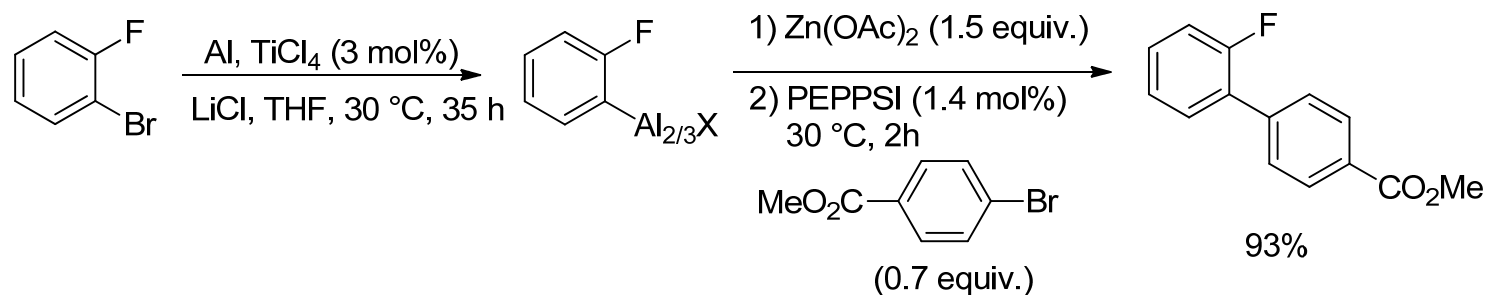
A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, 45, 6040.

Preparation of functionalized organometallics

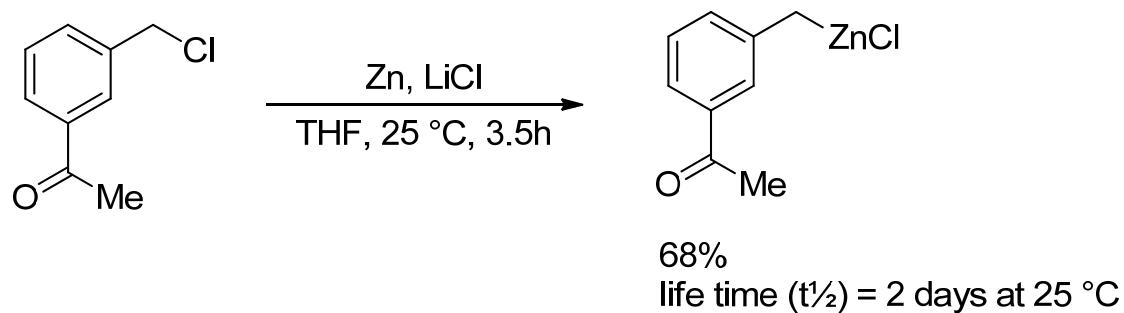


Preparation of functionalized organometallics

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

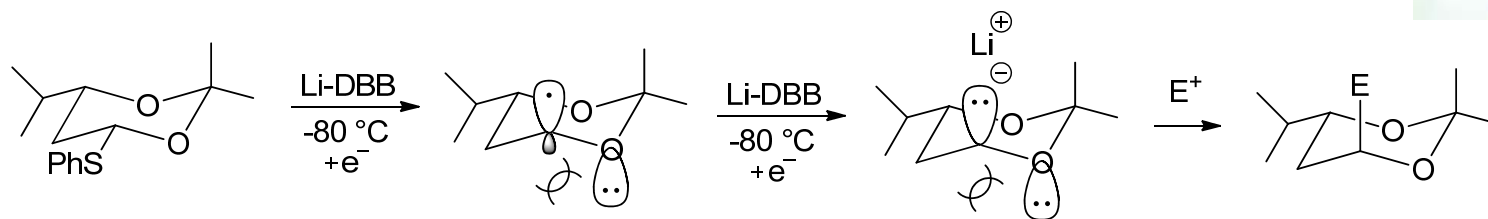
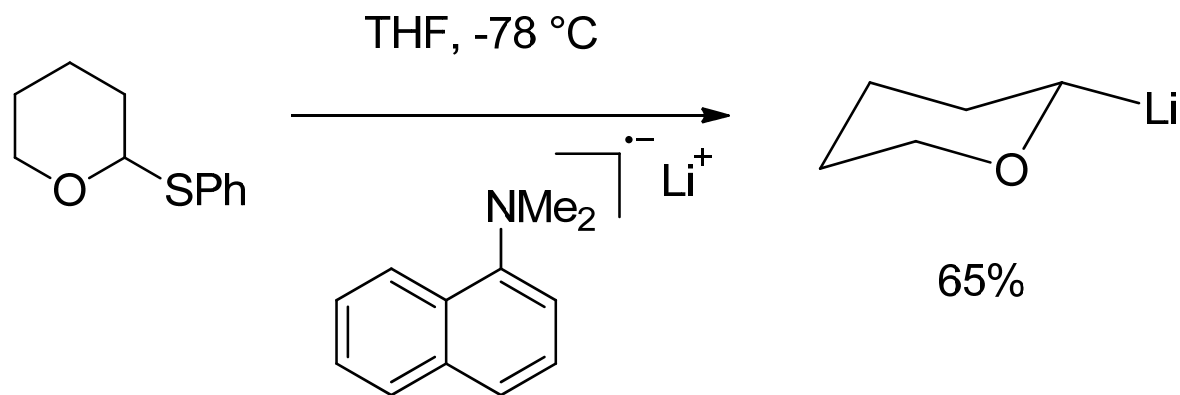


T. Blümke, Y.-H. Chen, P. Knochel *Nature Chemistry*, **2010**, 2, 313

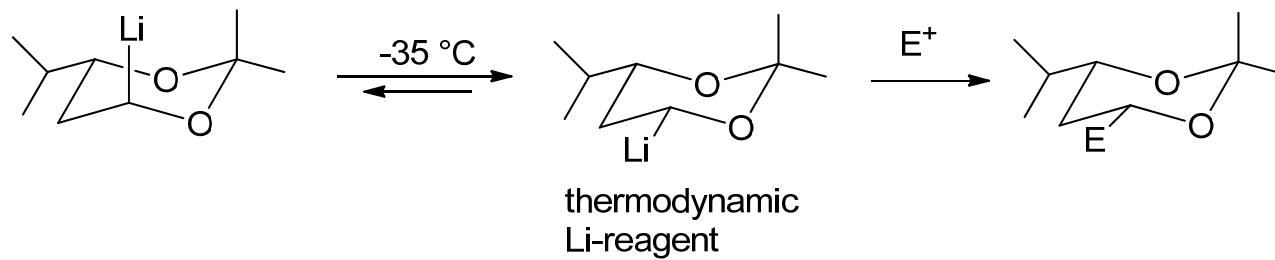


A. Metzger, P. Knochel *Org. Lett.* **2008**, 10, 1107

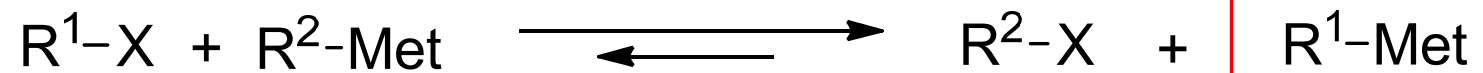
Extension to insertion reactions to C-S bonds



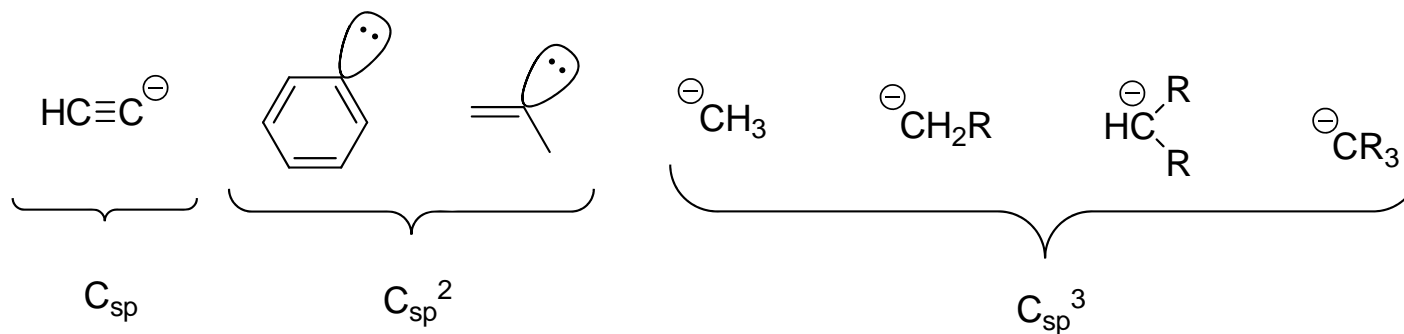
kinetic Li-reagent



The Halogen-Metal-Exchange

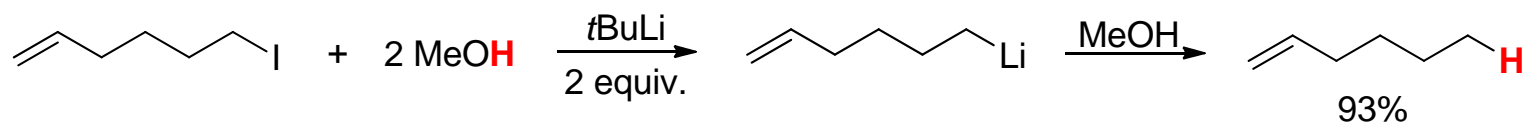
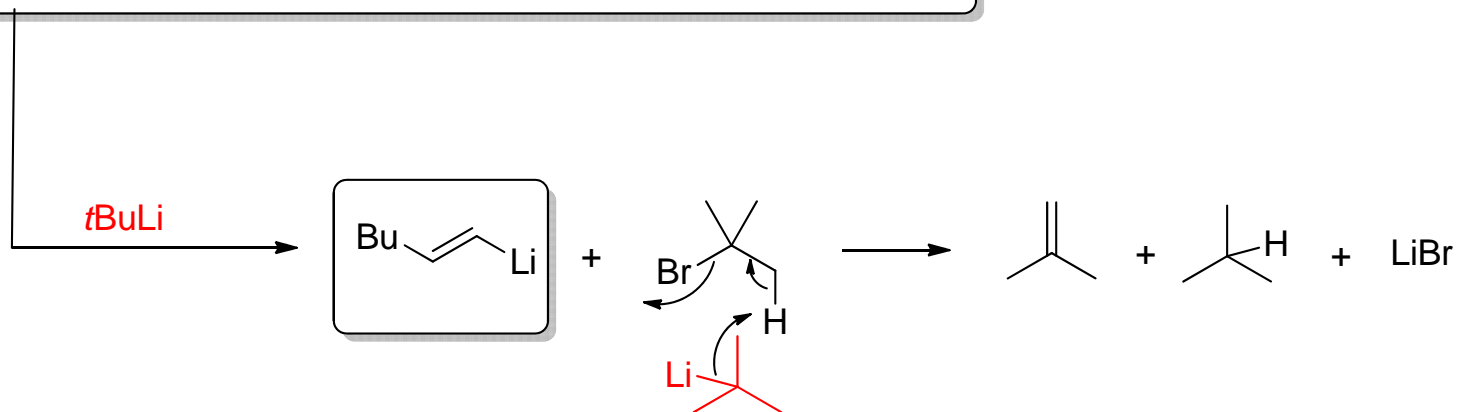
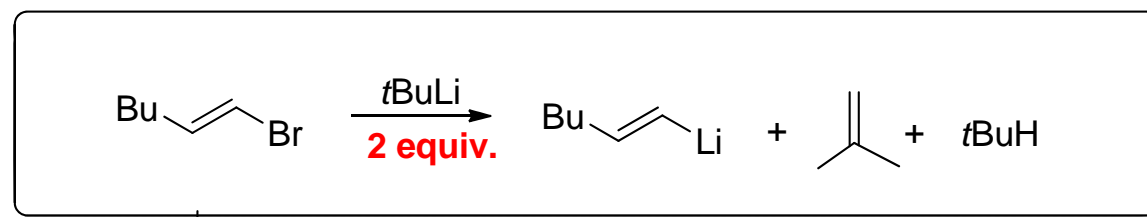
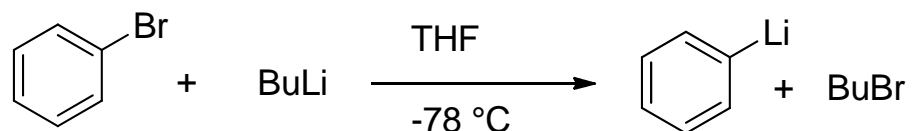


driving force: the most stable carbanion is always formed

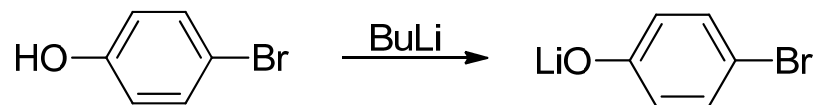


The Halogen-Metal-Exchange

1939: the Wittig-Gilman reaction



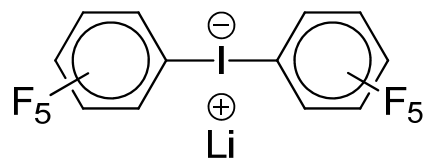
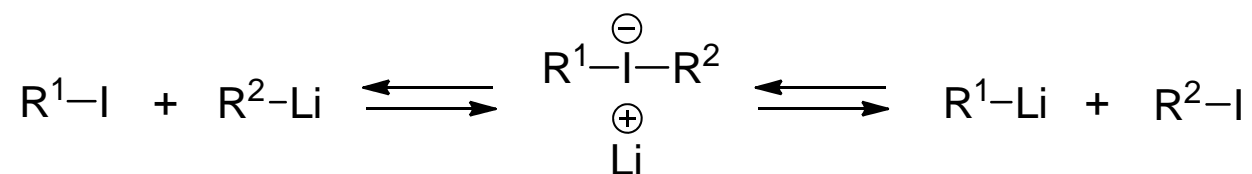
The Halogen-Metal-Exchange



I >> Br >> Cl

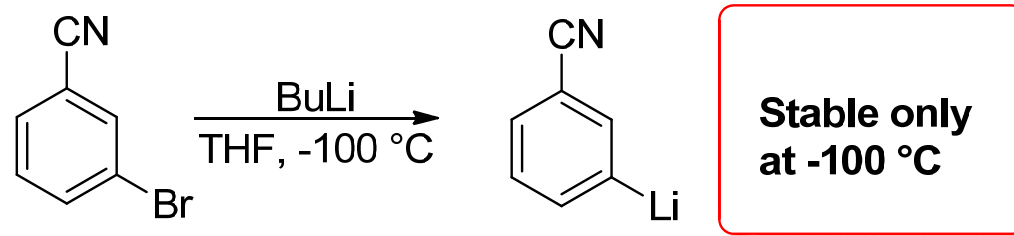
rate of the halogen/metal exchange

mechanism:

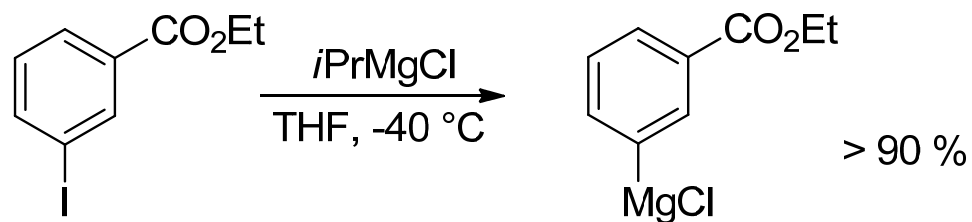


has been isolated

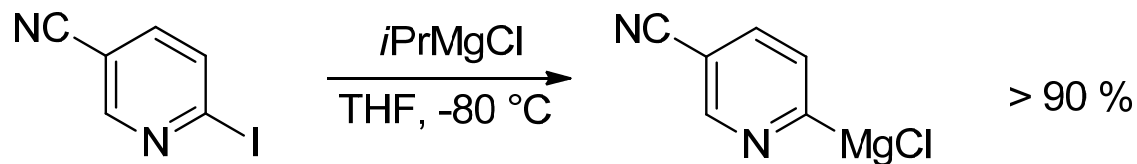
The Halogen-Metal-Exchange : tolerance of functional groups



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

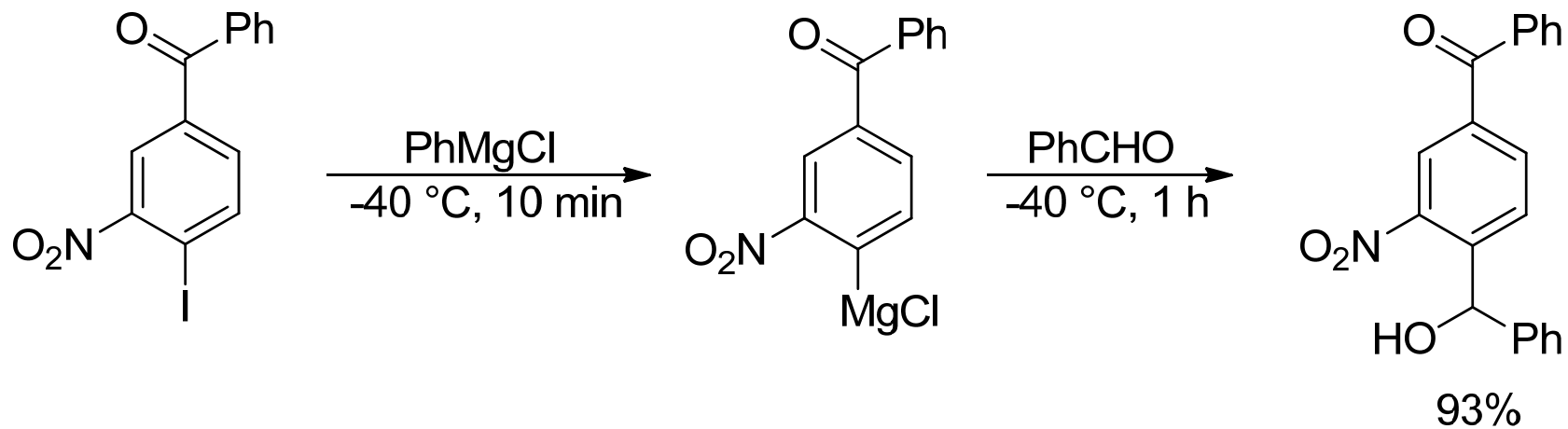


M. Rottländer, P. Knochel, Angew. Chem. Int. Ed. 1998, 40, 1801



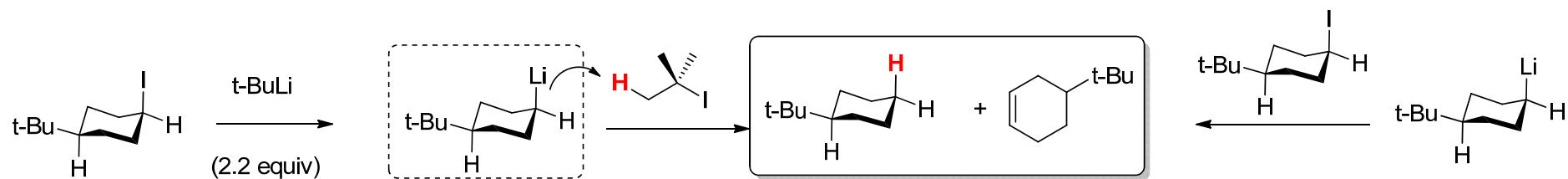
H. Ren, P. Knochel, Chem.Comm. **2006**, 726

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



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

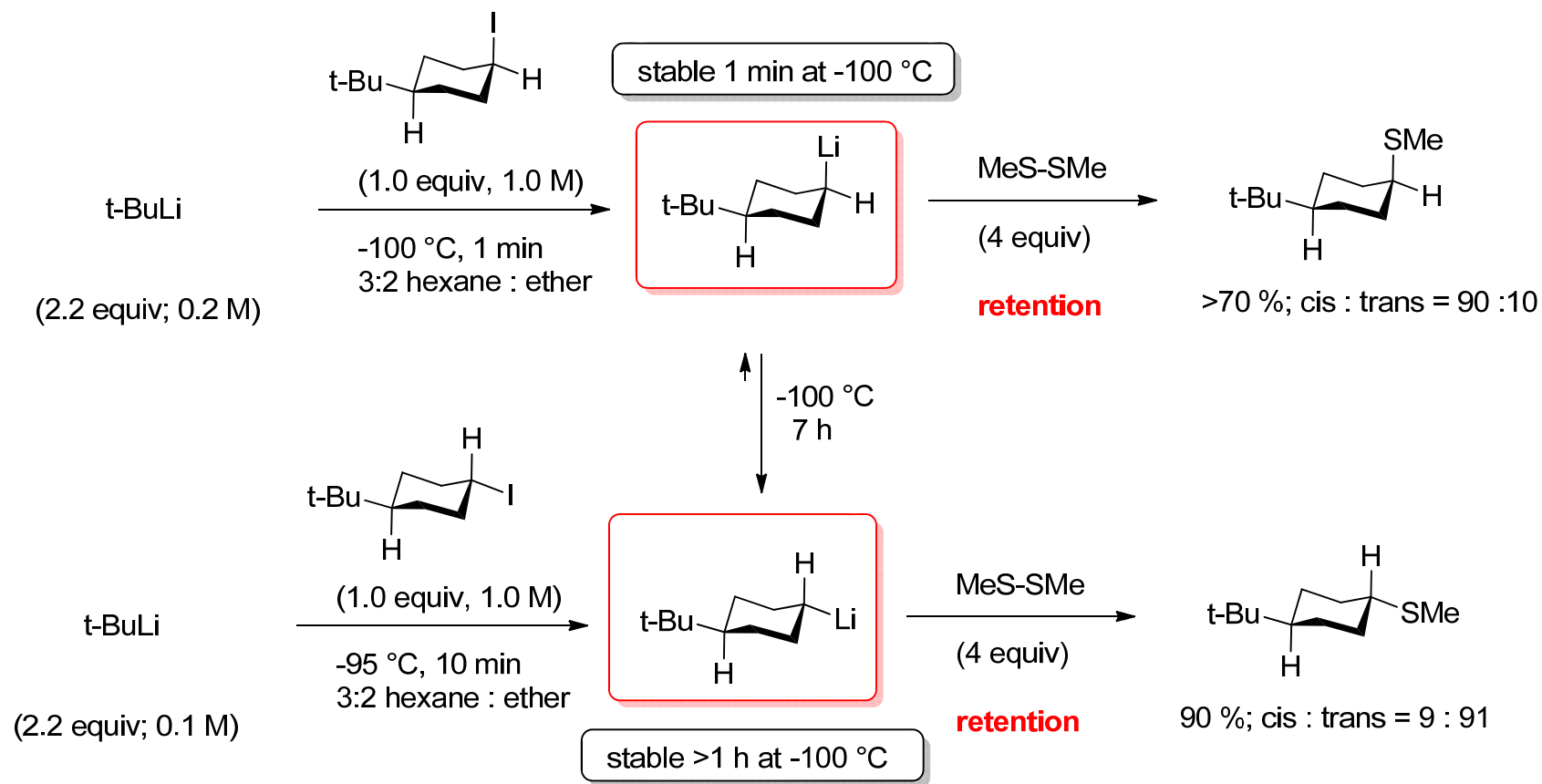
A secondary iodine/lithium exchange on cyclohexyl iodides



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

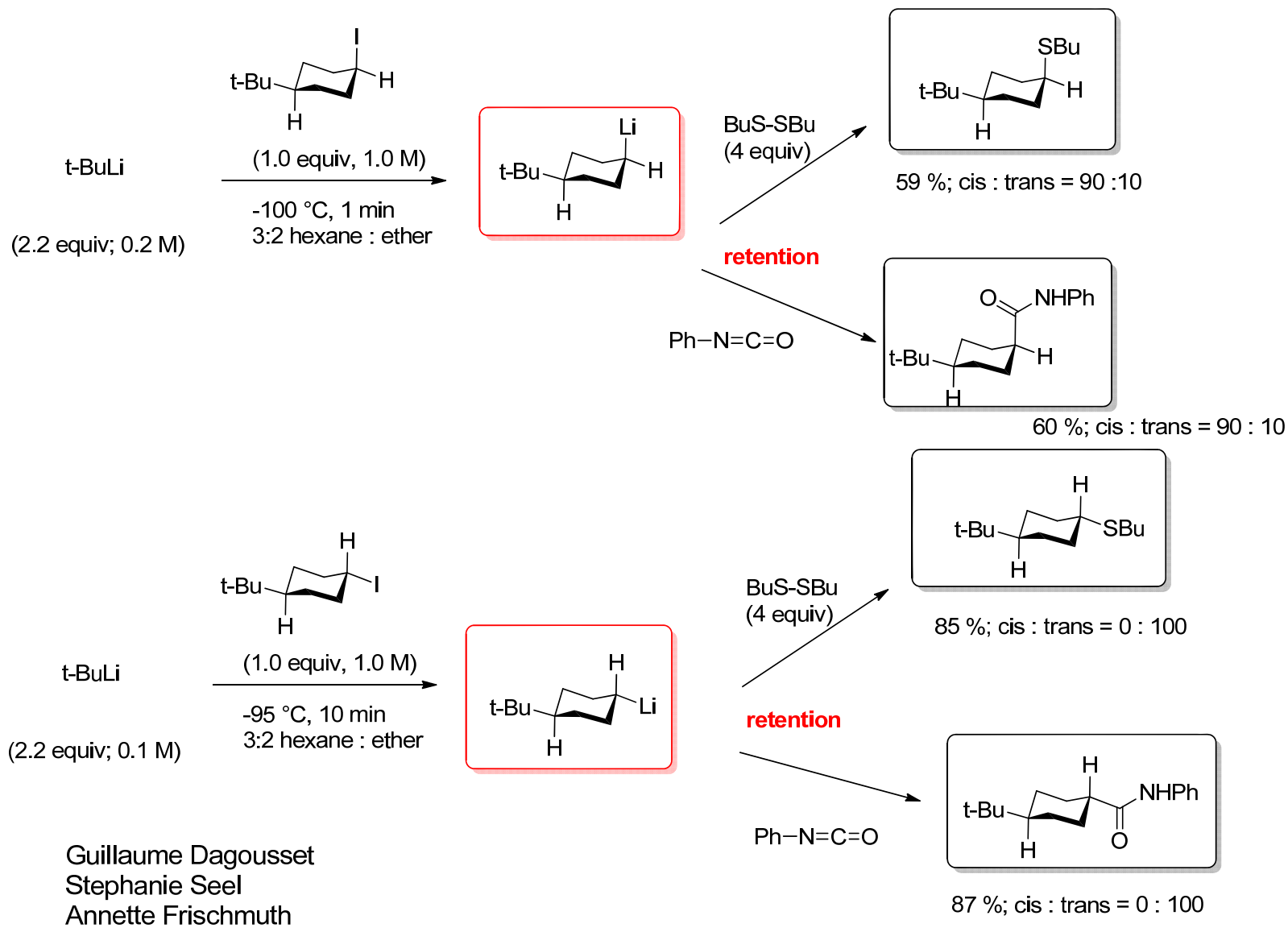
Stephanie SEEL

A secondary iodine/lithium exchange on cyclohexyl iodides

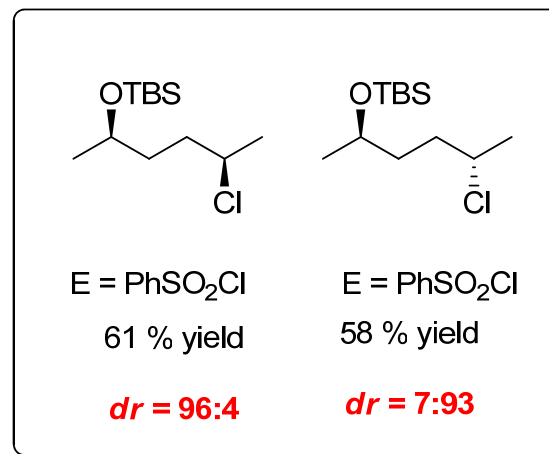
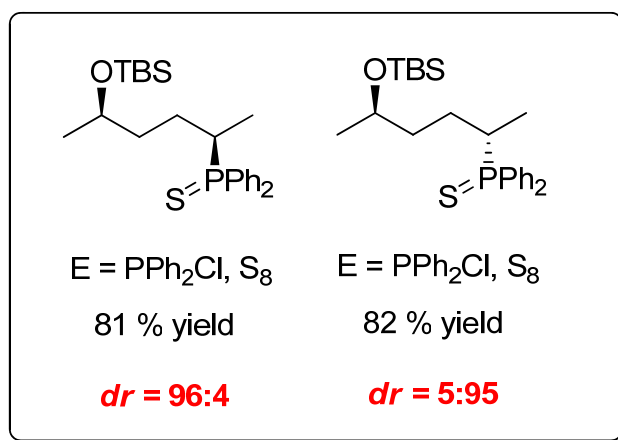
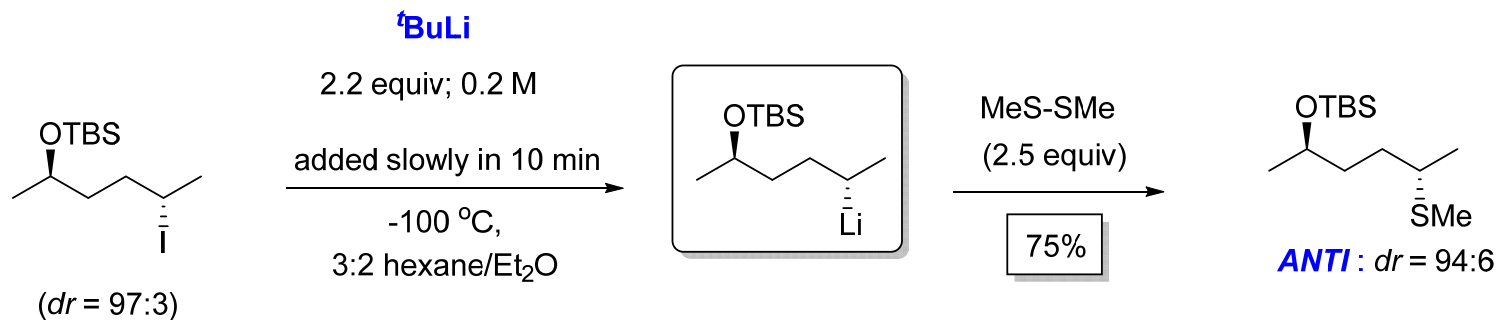
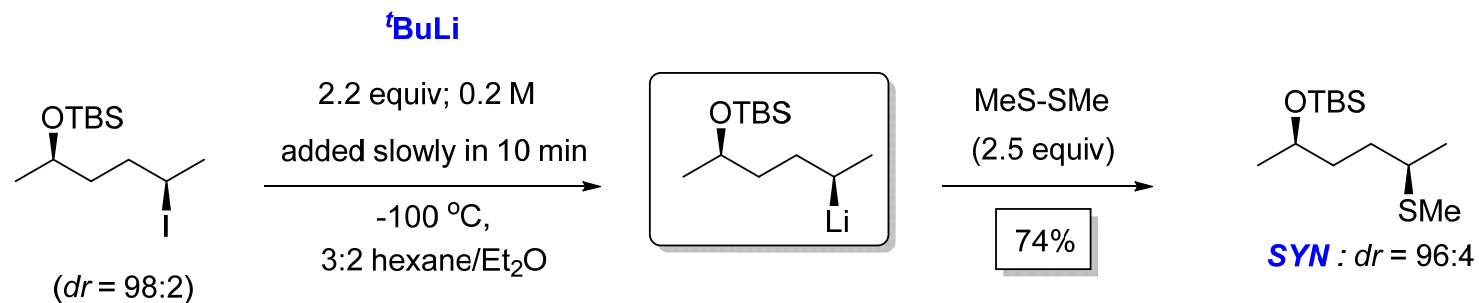


Stephanie SEEL

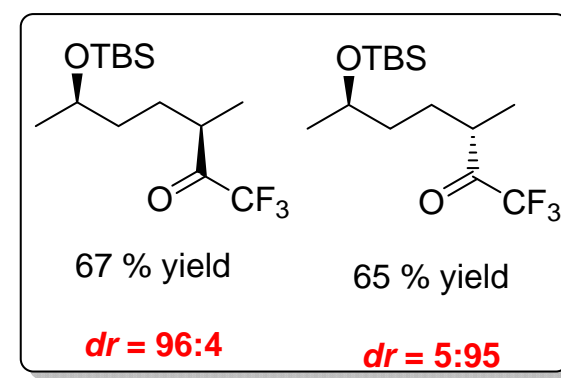
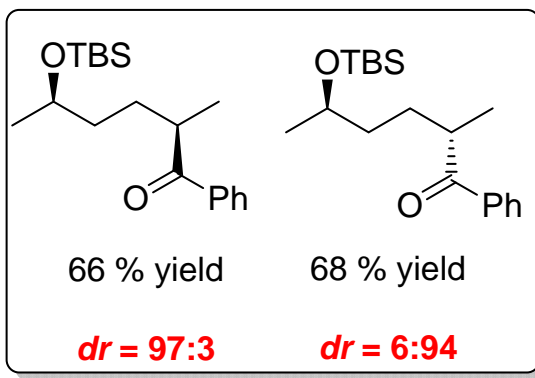
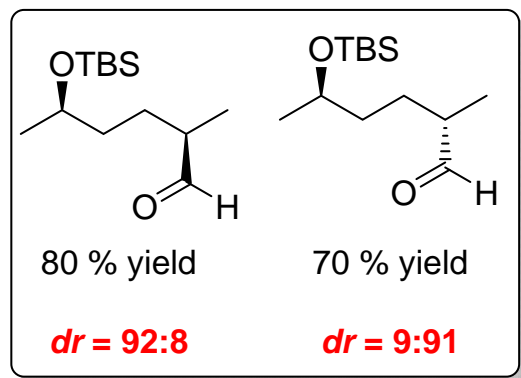
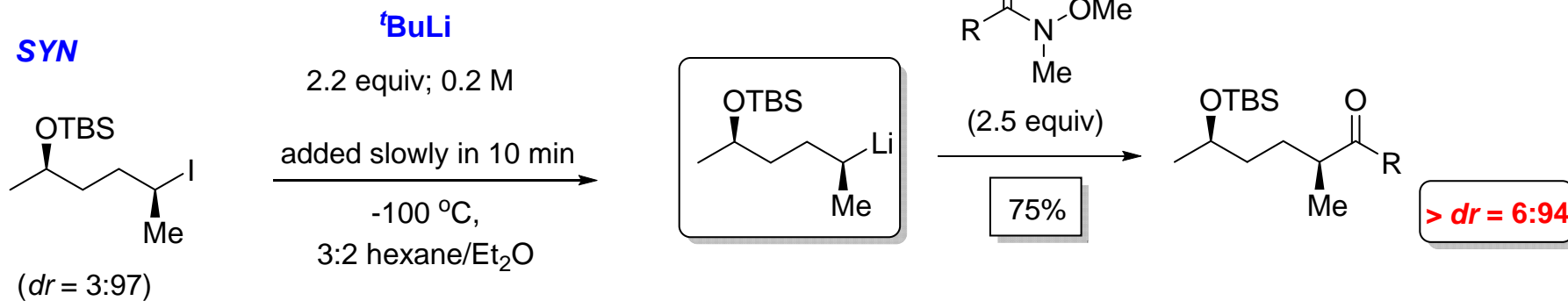
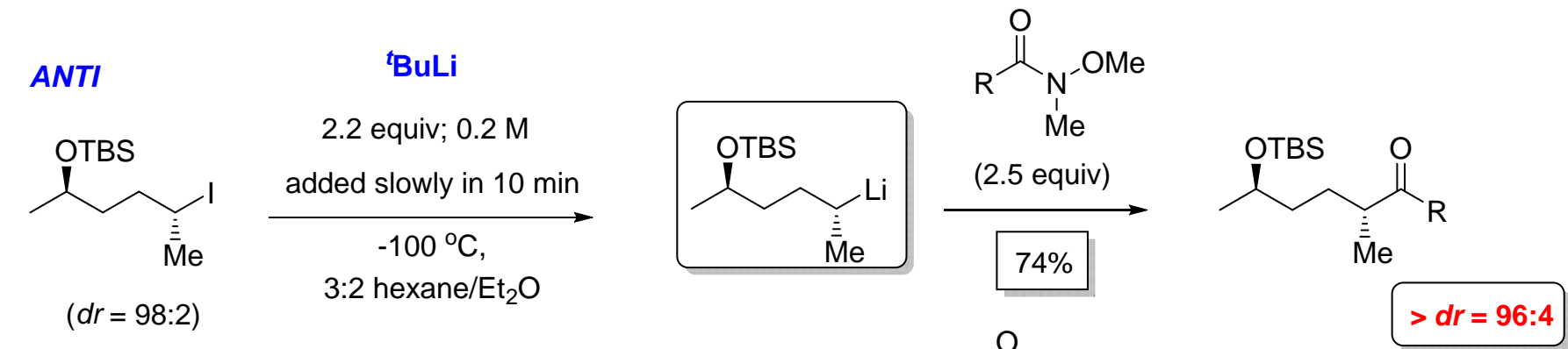
A secondary iodine/lithium exchange on cyclohexyl iodides



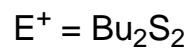
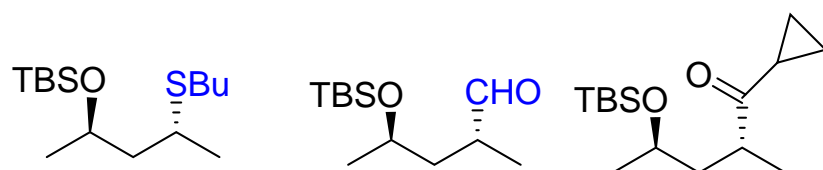
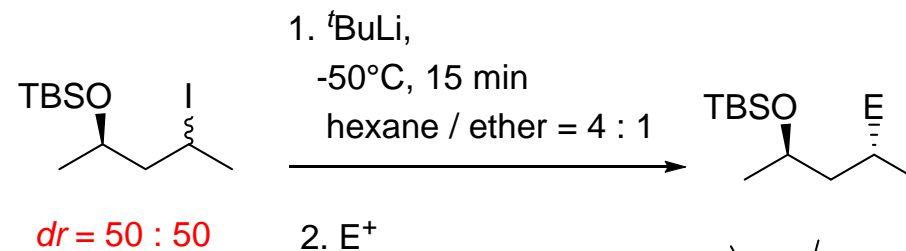
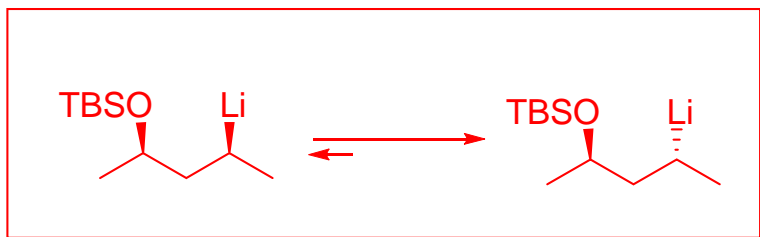
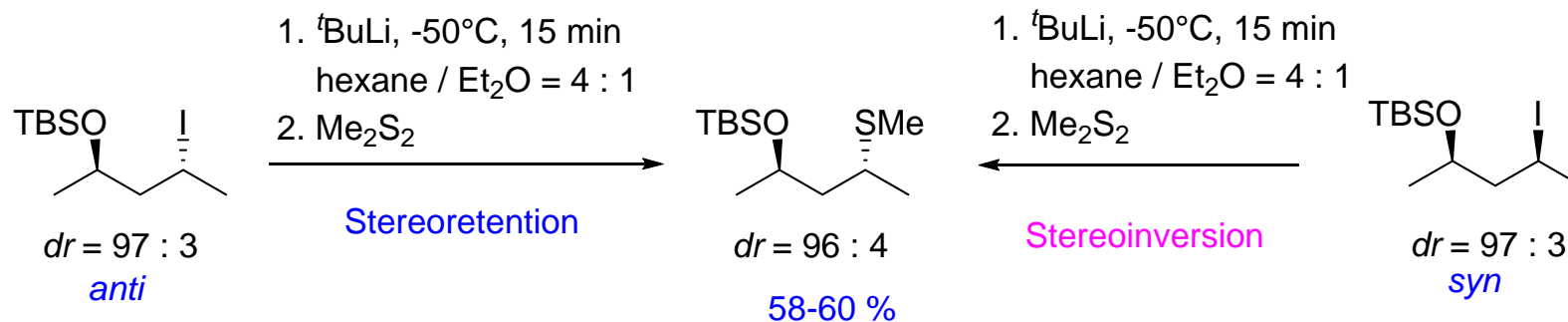
Acyclic systems: stereospecific I/Li exchange reaction



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

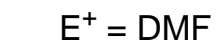


Stereoconvergent synthesis of Li-reagents



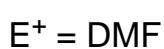
60 %

$dr = 94 : 6$



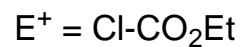
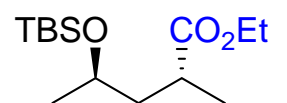
74 %

$dr = 92 : 8$



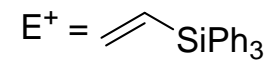
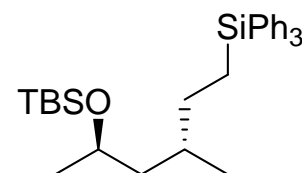
67 %

$dr = 96 : 4$



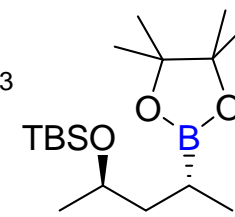
67 %

$dr = 96 : 4$



63 %

$dr = 99 : 1$



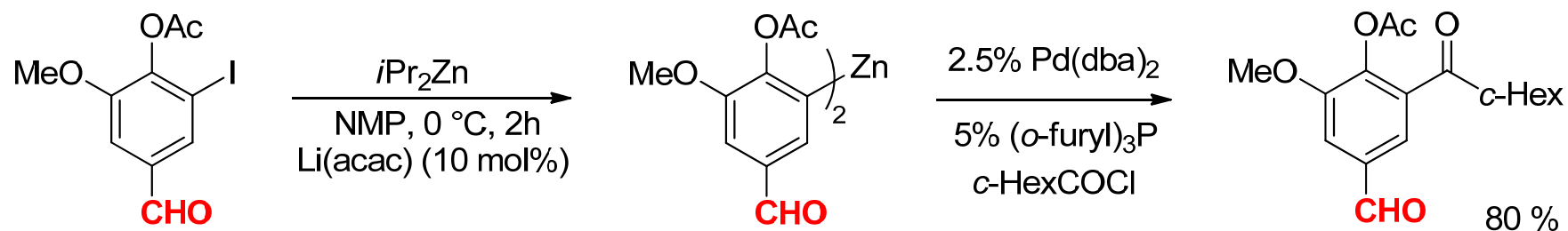
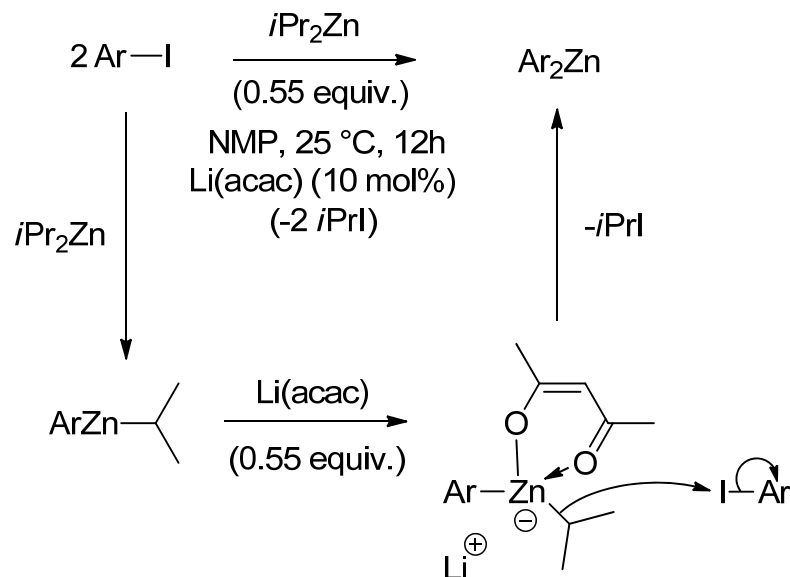
73 %

$dr = 97 : 3$

D. Didier, K. Moriya, 2014

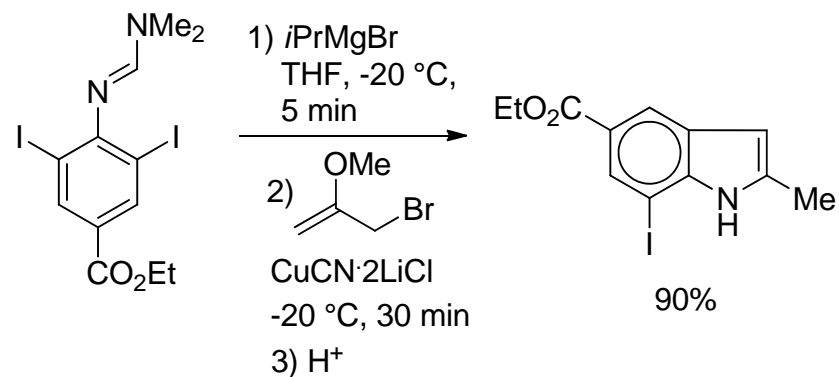
The iodine/zinc-exchange

catalysis of the halogen-metal exchange

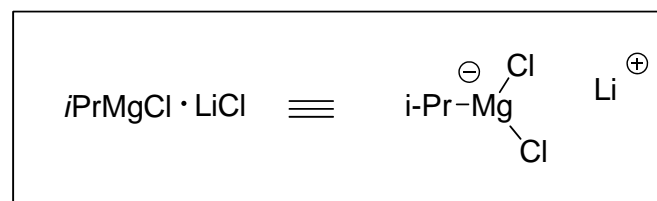
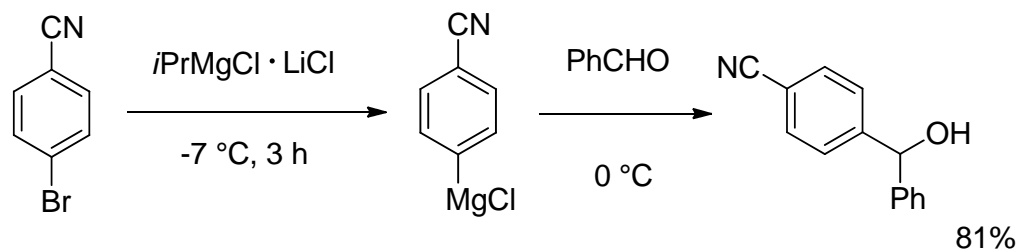


The Halogen-Metal-Exchange

indole-synthesis

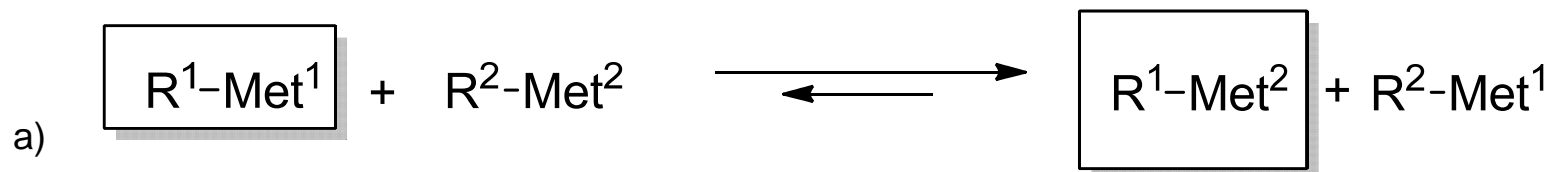


D. M. Lindsay, W. Dohle, A. E. Jensen, F. Kopp, P. Knochel *Org. Lett.*, **2002**, 4, 1819

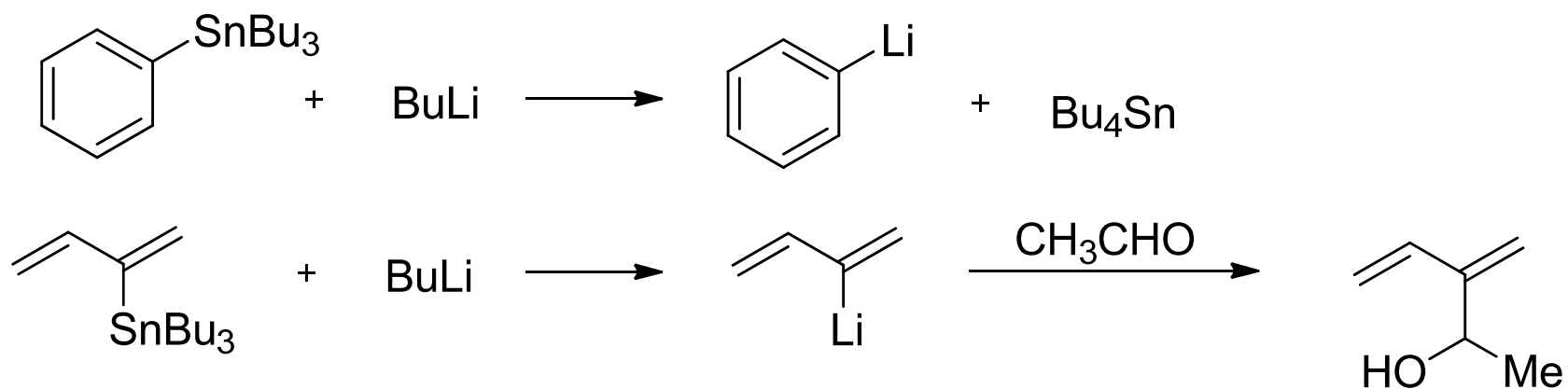


A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2004**, 43, 3333

Transmetalation

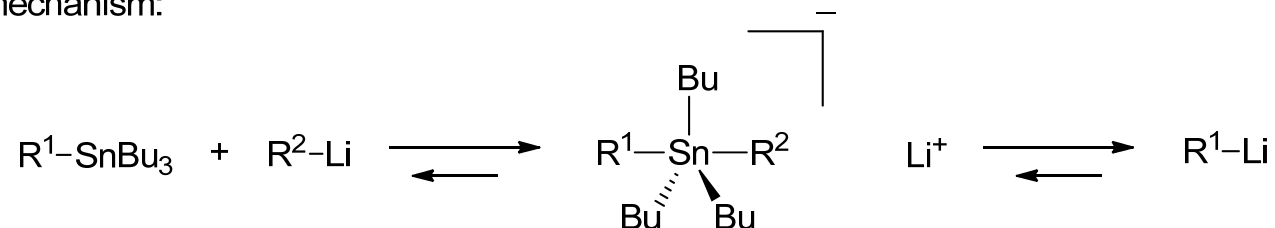


the most stable carbanion is linked to the most electropositive metal

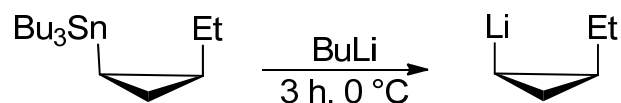


Transmetalation

mechanism:



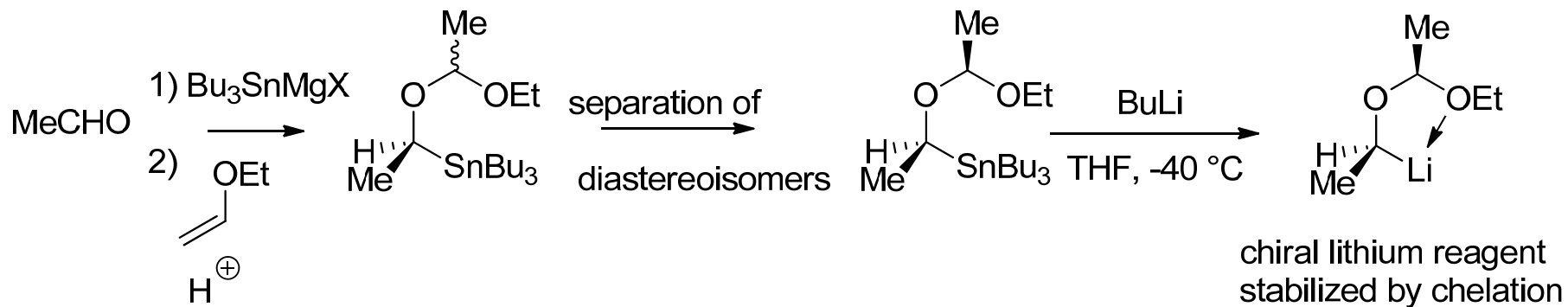
the most stable Li-organometallic is formed



configurational stable

Li-reagent due to the ring strain

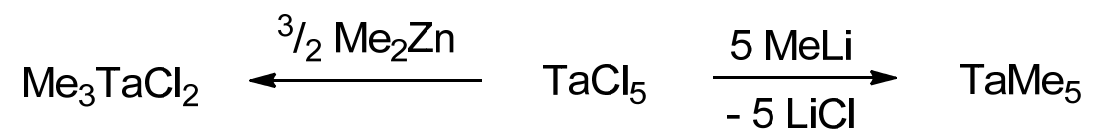
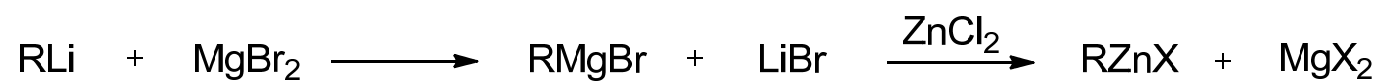
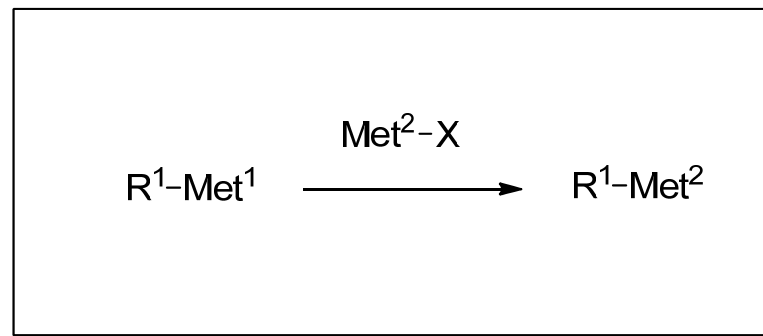
E. J. Corey Tetrahedron Lett. 1984, 25, 2415



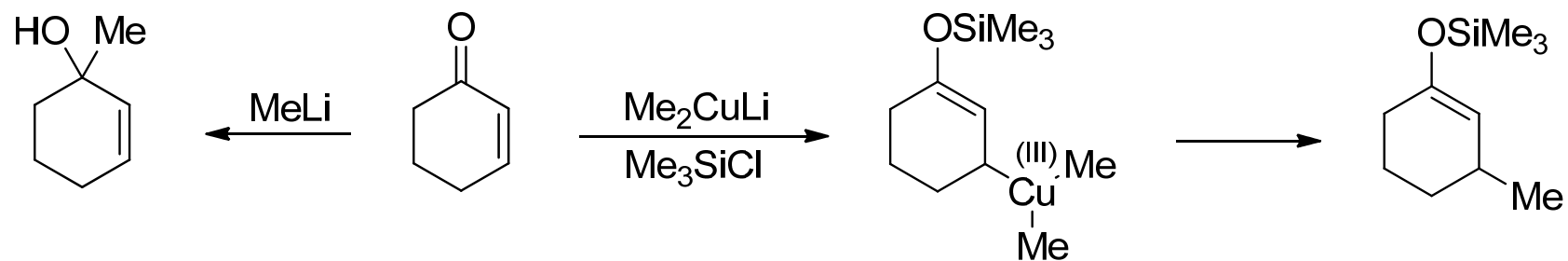
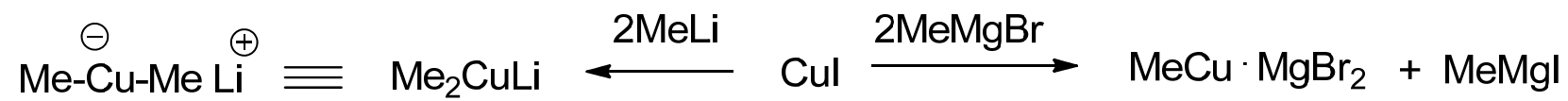
W. C. Still, *J. Am. Chem. Soc.* **1980**, 102, 1201

Transmetalation

b)



Transmetalation

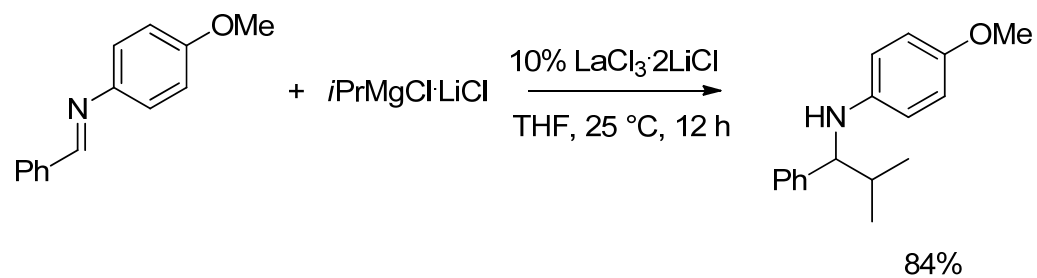
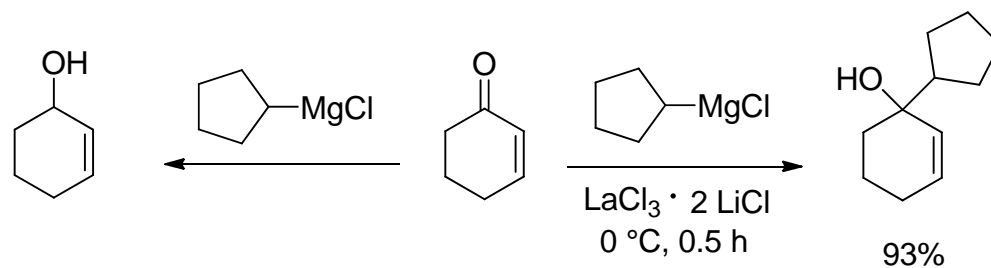
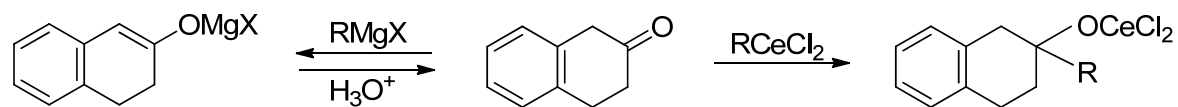


E. Nakamura, I. Kuwajima *J. Am. Chem. Soc.* **1984**, *106*, 3368

Transmetalation

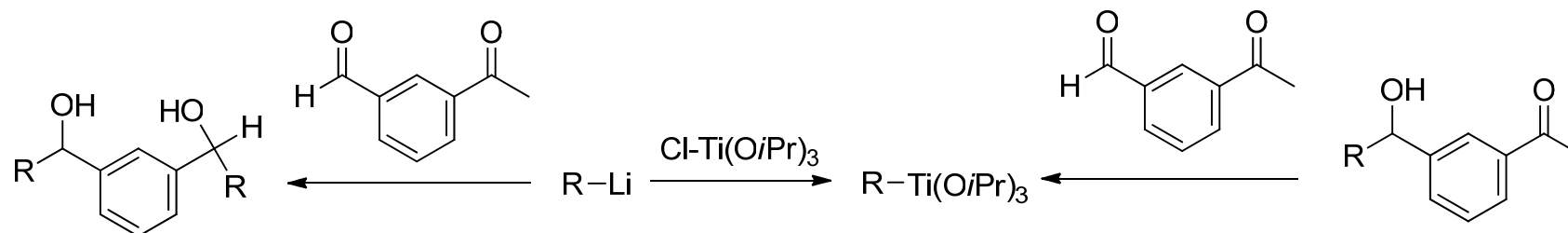


T. Imamoto, Y. Sugiyura, N. Takiyama, *Tetrahedron Lett.* **1984**, 25, 4233

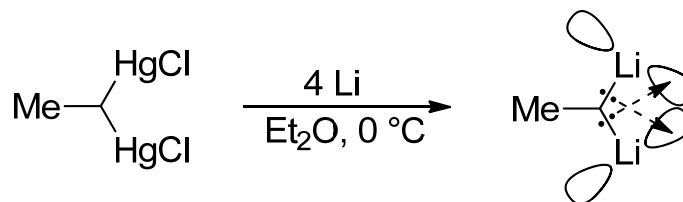


A. Krasovskiy, F. Kopp, P. Knochel *Angew. Chem. Int. Ed.* **2006**, 45, 497

Transmetalation



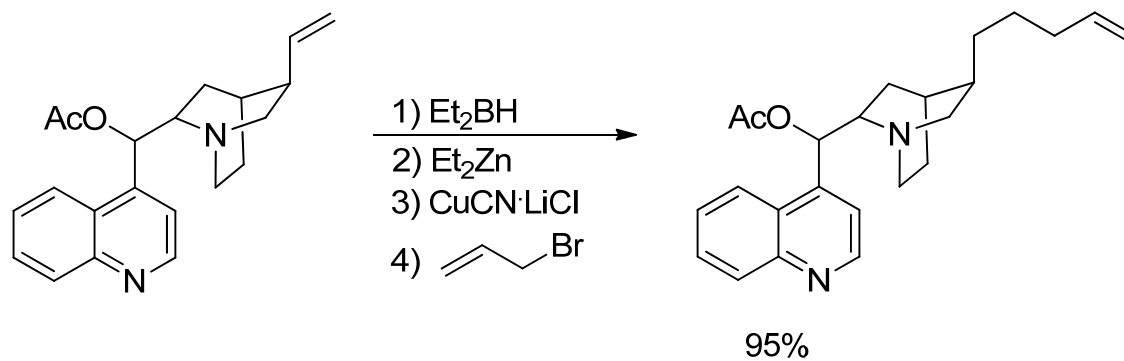
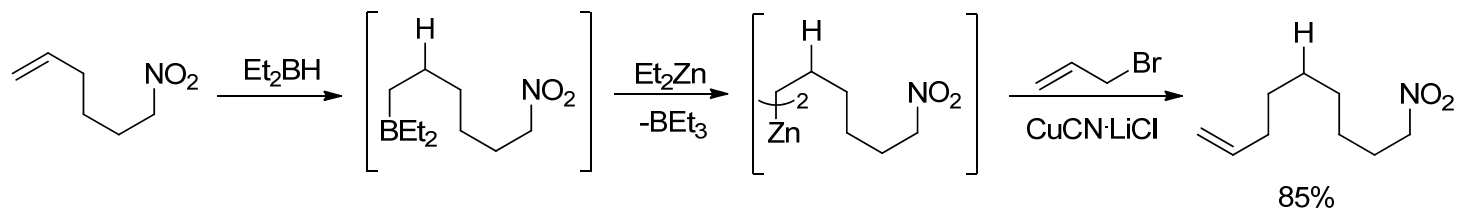
M. Reetz, D. Seebach *Angew. Chem.* **1983**, *95*, 12



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

Transmetalation

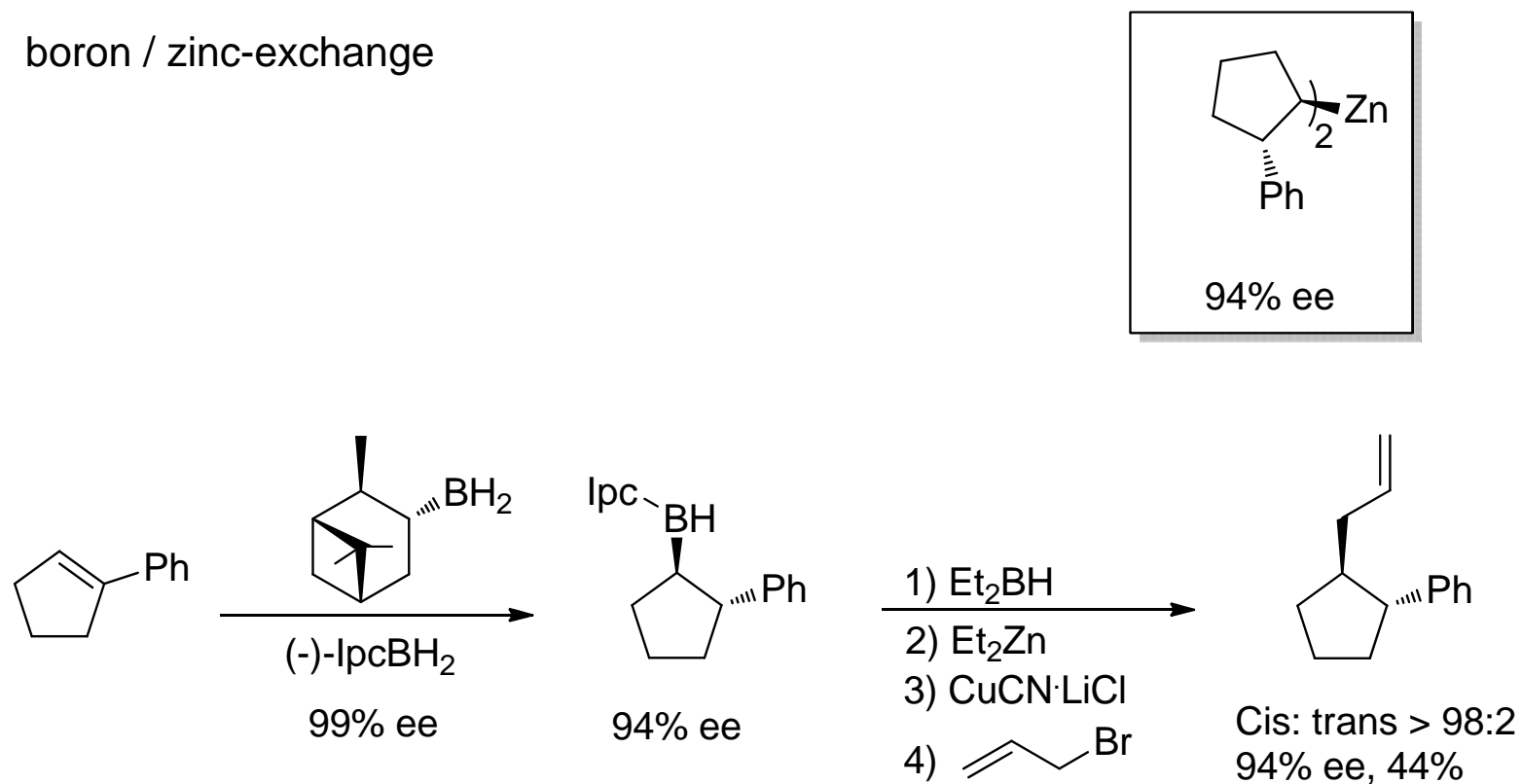
boron / zinc-exchange



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

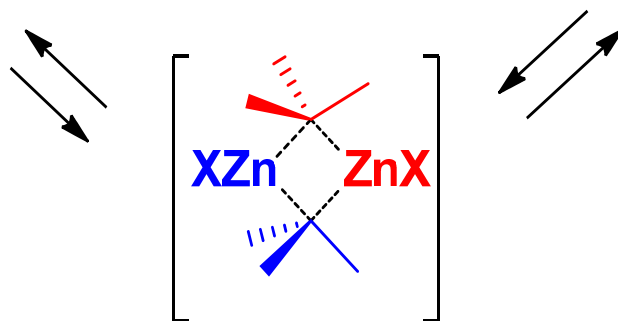
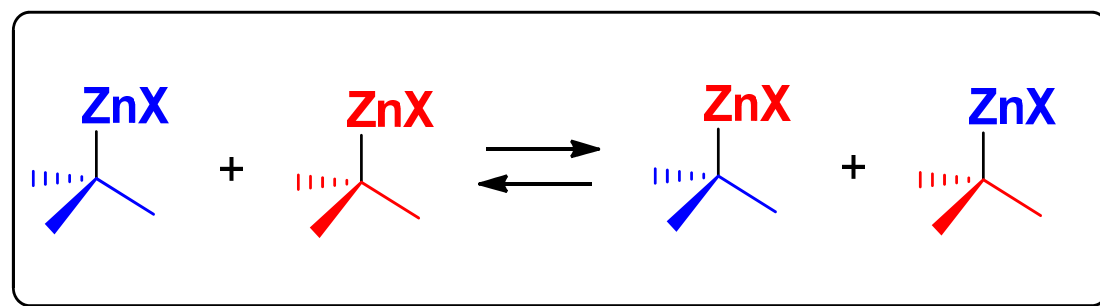
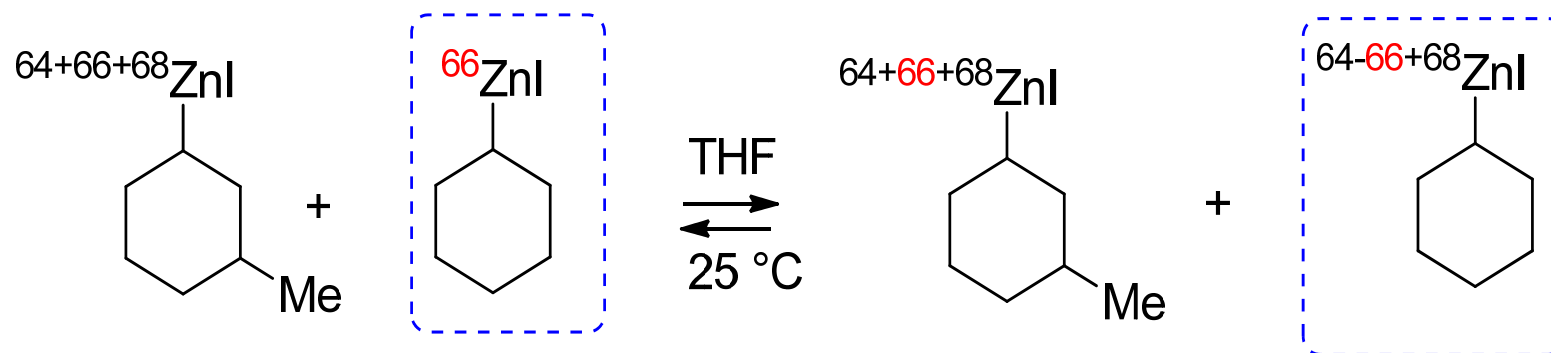
Transmetalation

boron / zinc-exchange

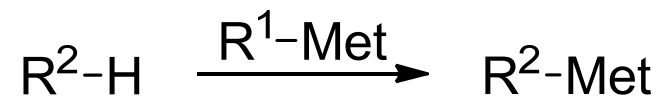


L. Micouin, M. Oestreich, P. Knochel *Angew. Chem. Int. Ed.* **1997**, 36, 245

Nature of the carbon-zinc bond



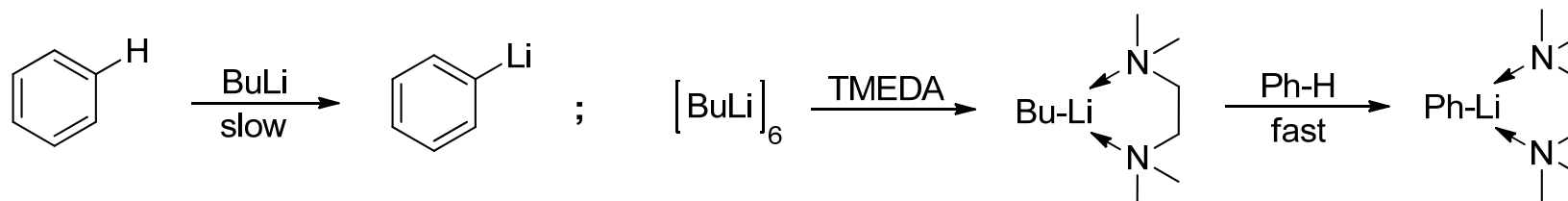
Metalation (starting from a compound with an acid proton)



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, ...

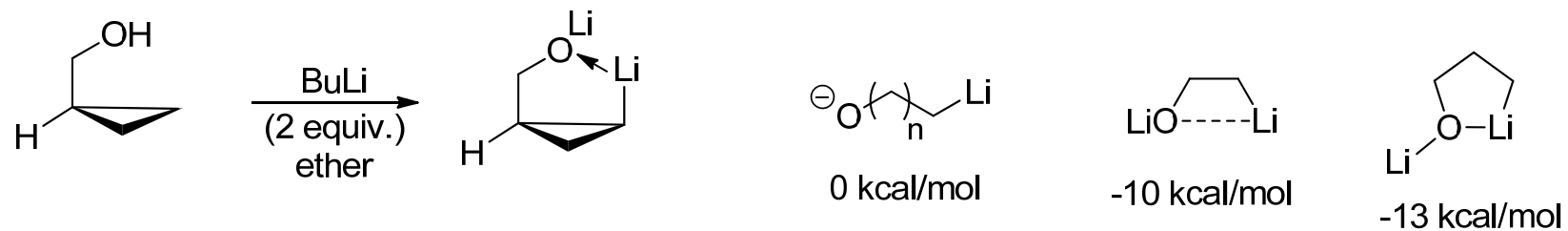
kinetic criteria (kinetic acidity)



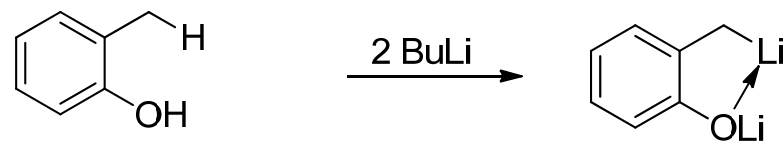
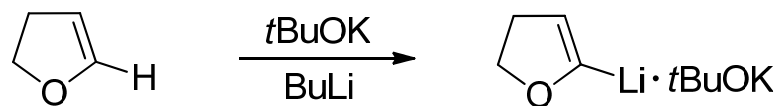
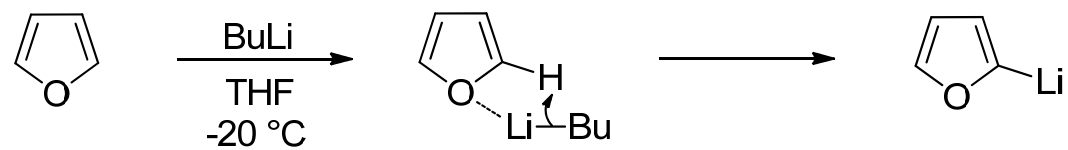
PhCH₂Li reacts with benzene 10⁴ times faster than with MeLi

PhCH₂Li is a monomer in THF, MeLi a tetramer

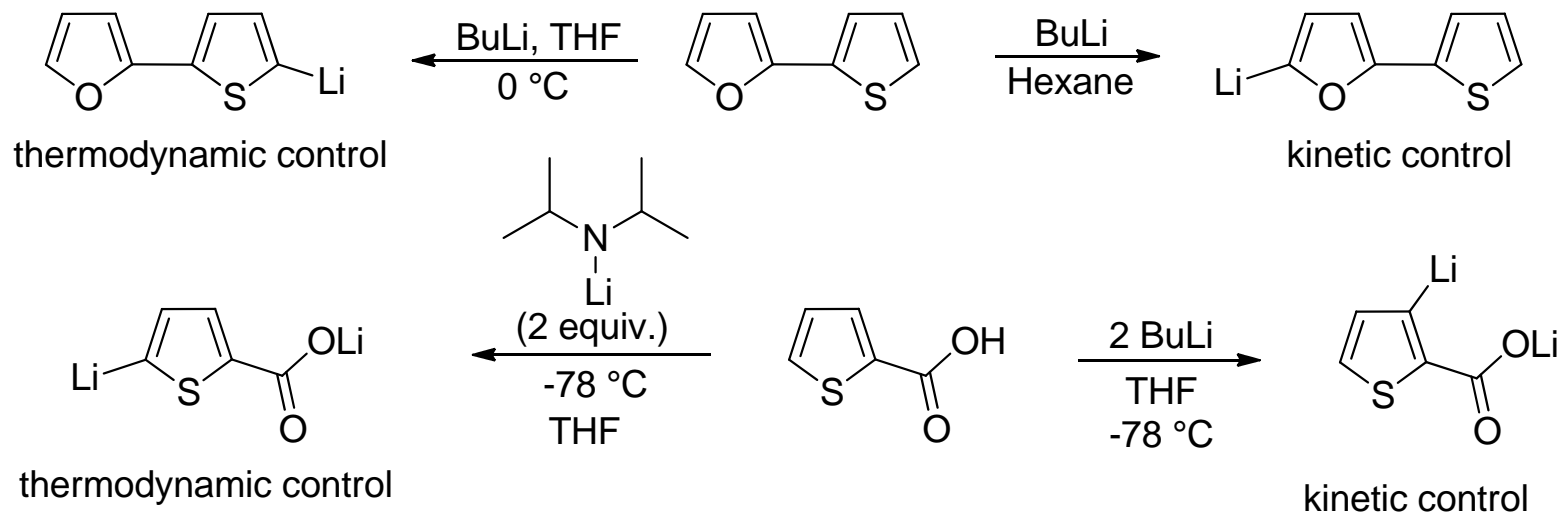
Directed metalation



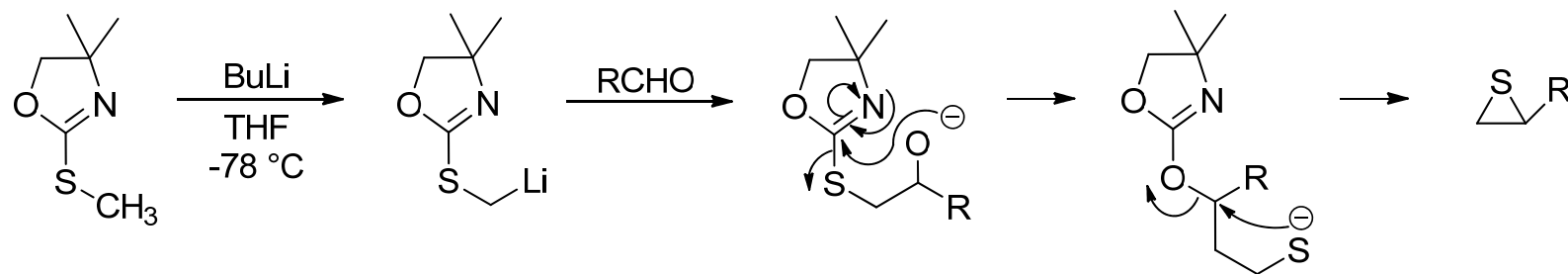
Directed metalation



Metalation

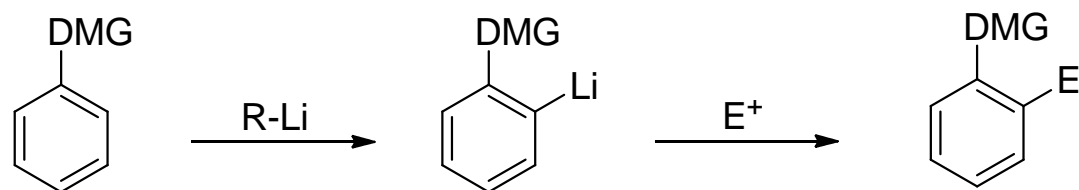


rearrangement



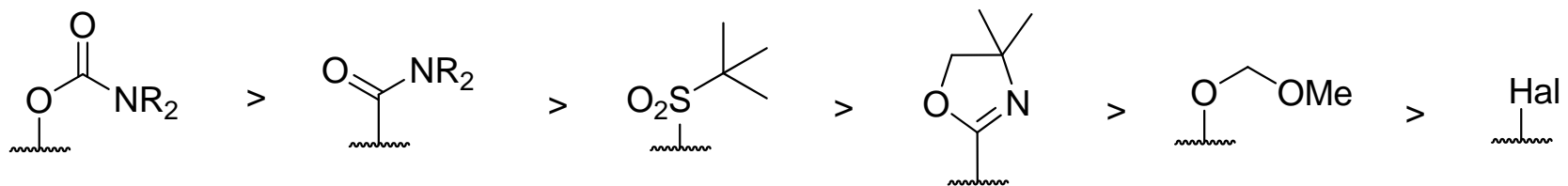
Metalation

directed lithiation



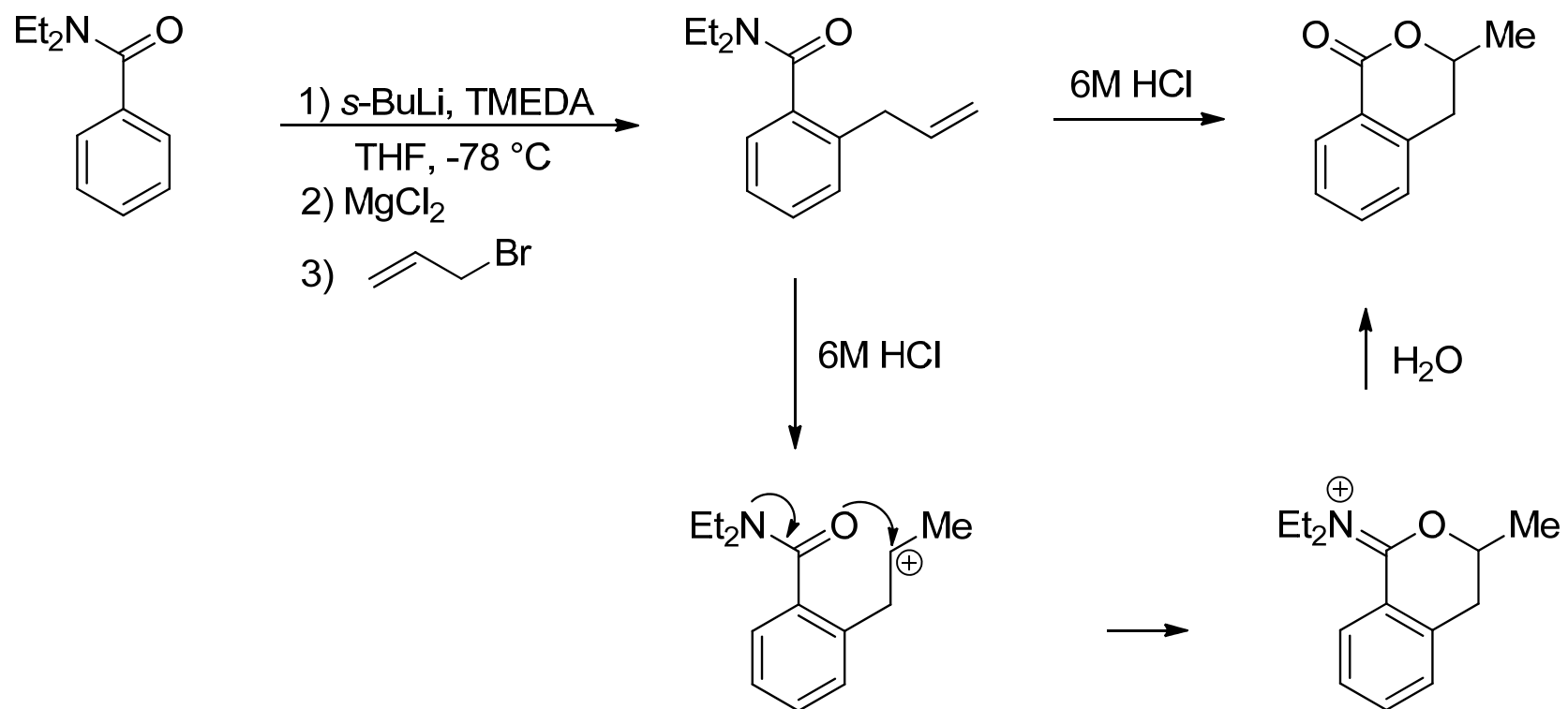
DMG = directing metalating group

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

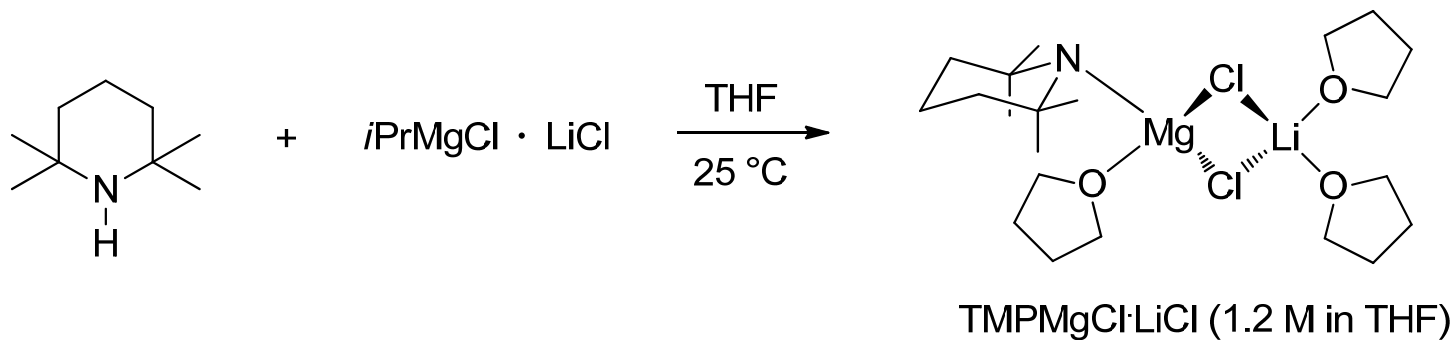


P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206

Metalation

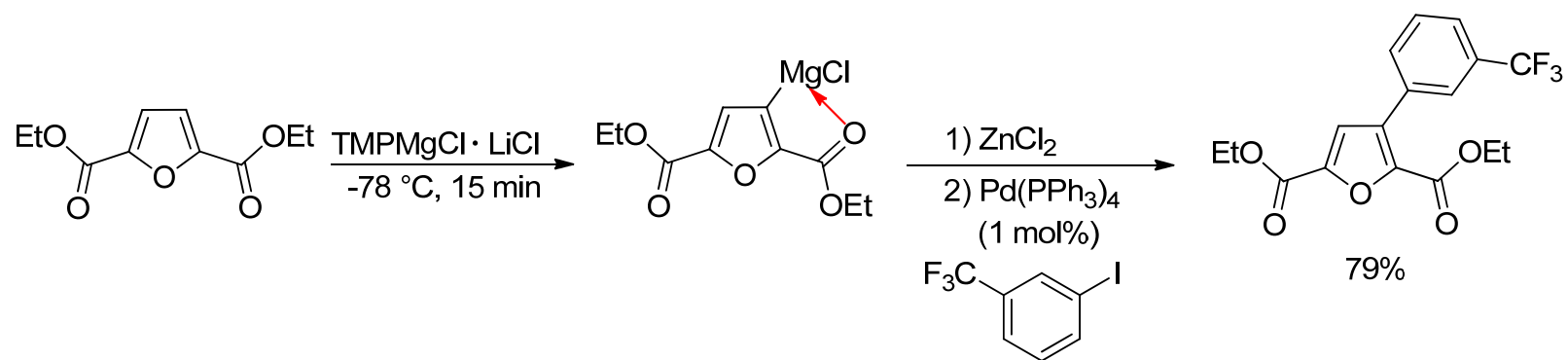


Metalation



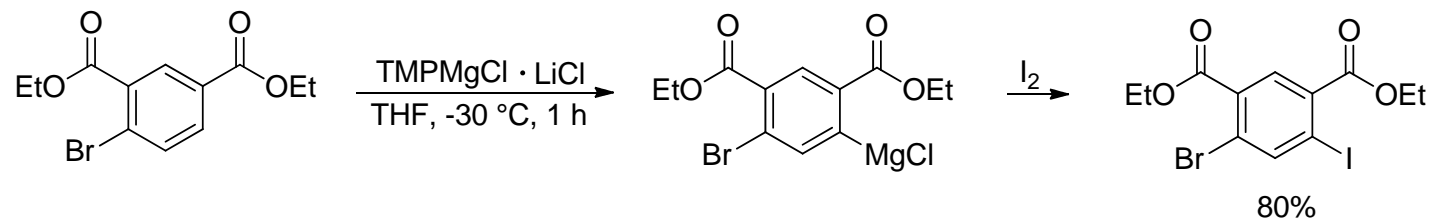
A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2006**, *45*, 2958

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

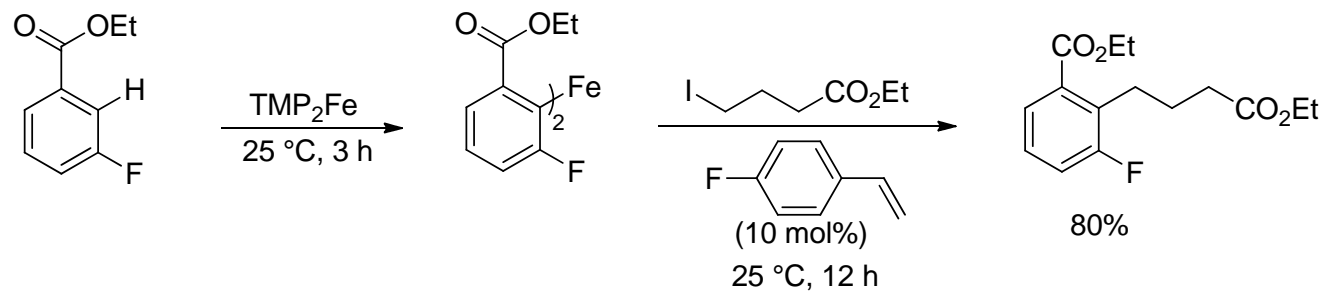
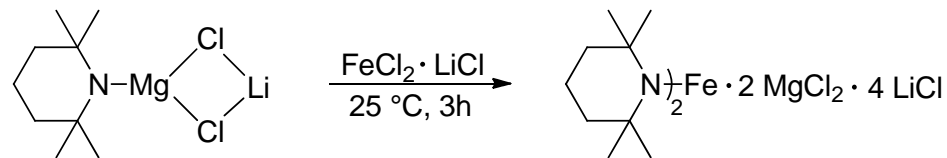


F. M. Piller, P. Knochel *Org. Lett.* **2009**, *11*, 445

Metalation

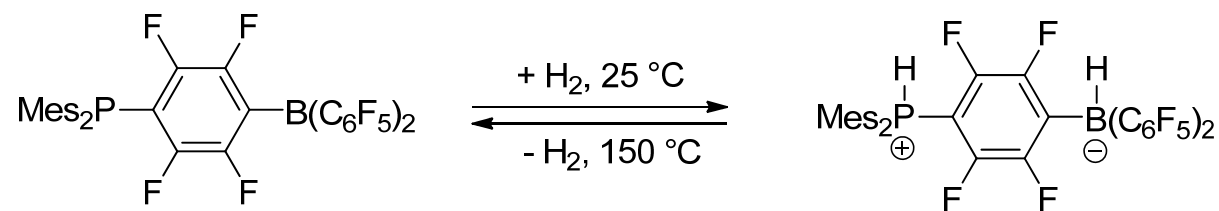


O. Baron, P. Knochel *Angew. Chem. Int. Ed.* **2006**, 45, 2958

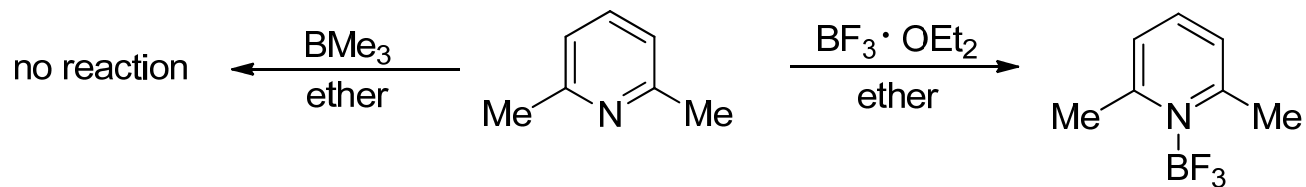


S. Wunderlich, P. Knochel *Angew. Chem. Int. Ed.* **2009**, 48, 9717

Frustrated Lewis Pairs

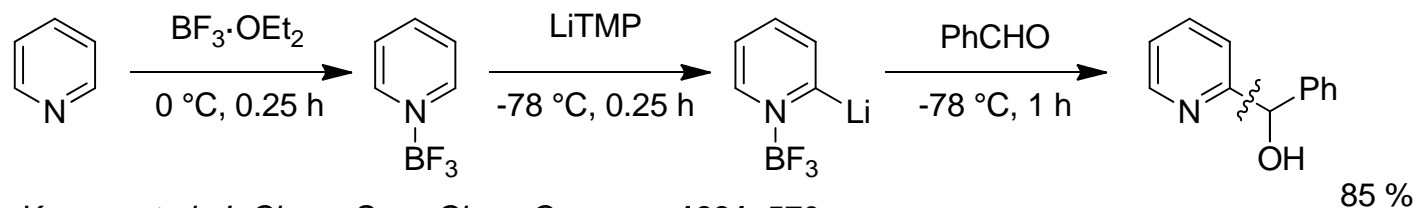


D. Stefan, G. Erker *Angew. Chem. Int. Ed.* **2010**, *49*, 46

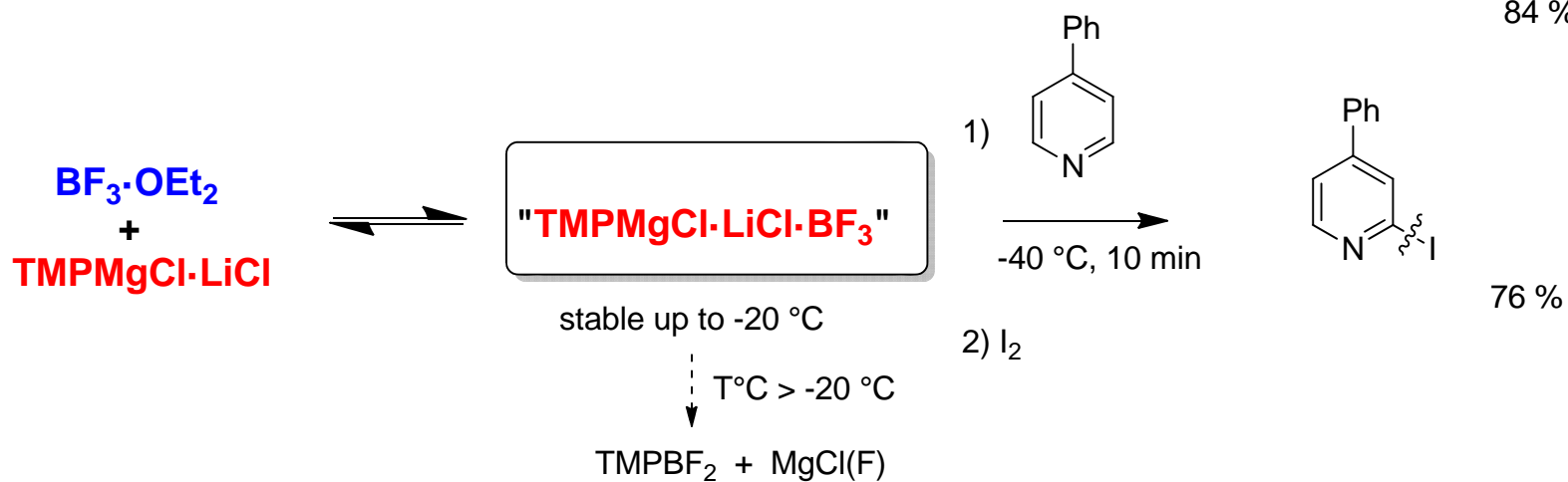
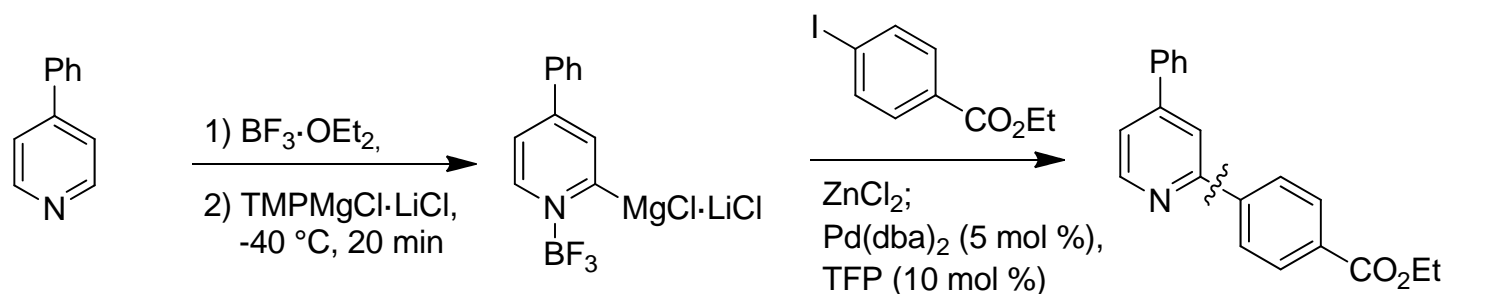


H. C. Brown *J. Am. Chem. Soc.* **1942**, *64*, 325

Frustrated Lewis Pairs

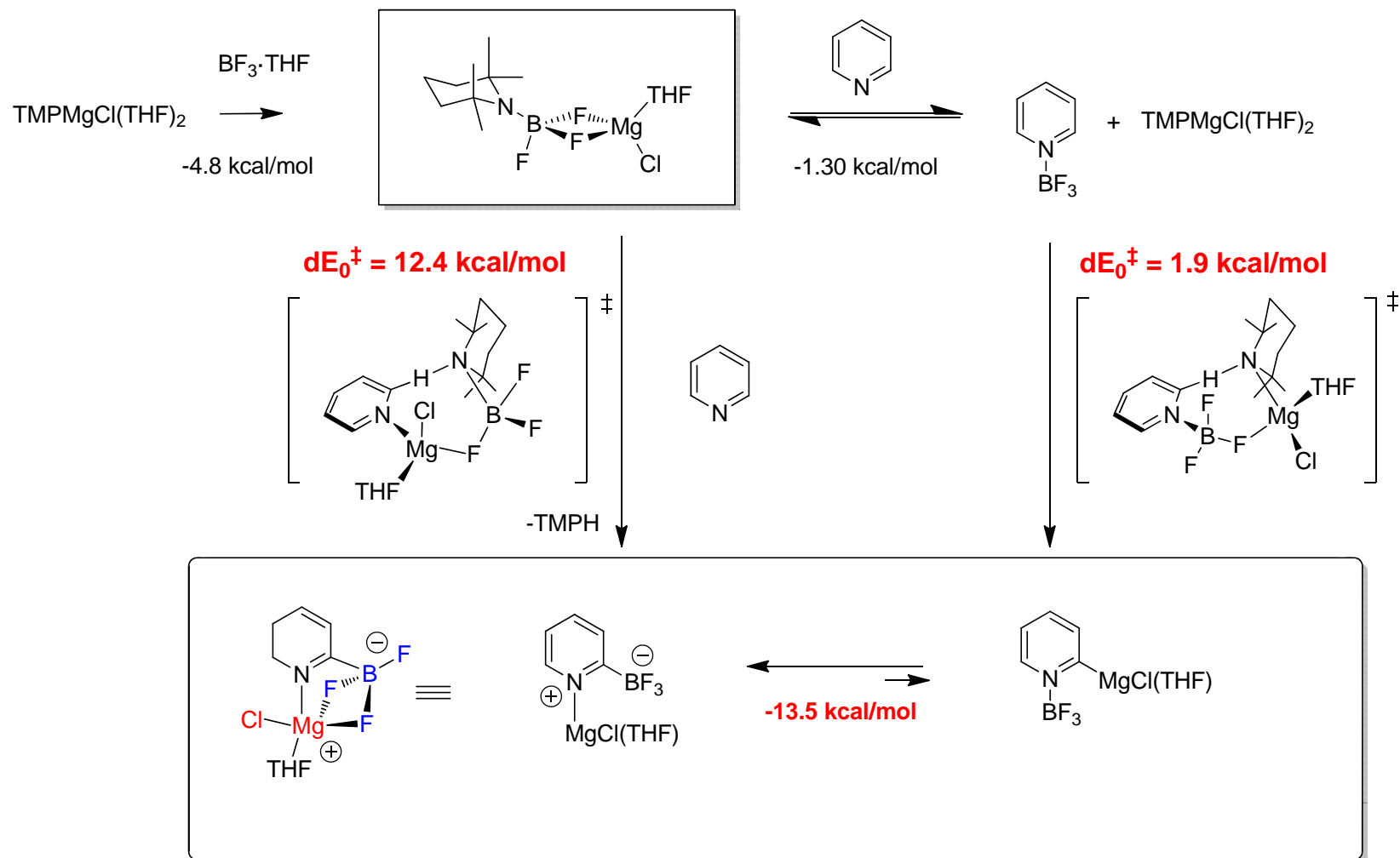


Kessar *et al*, *J. Chem. Soc., Chem Commun.* **1991**, 570

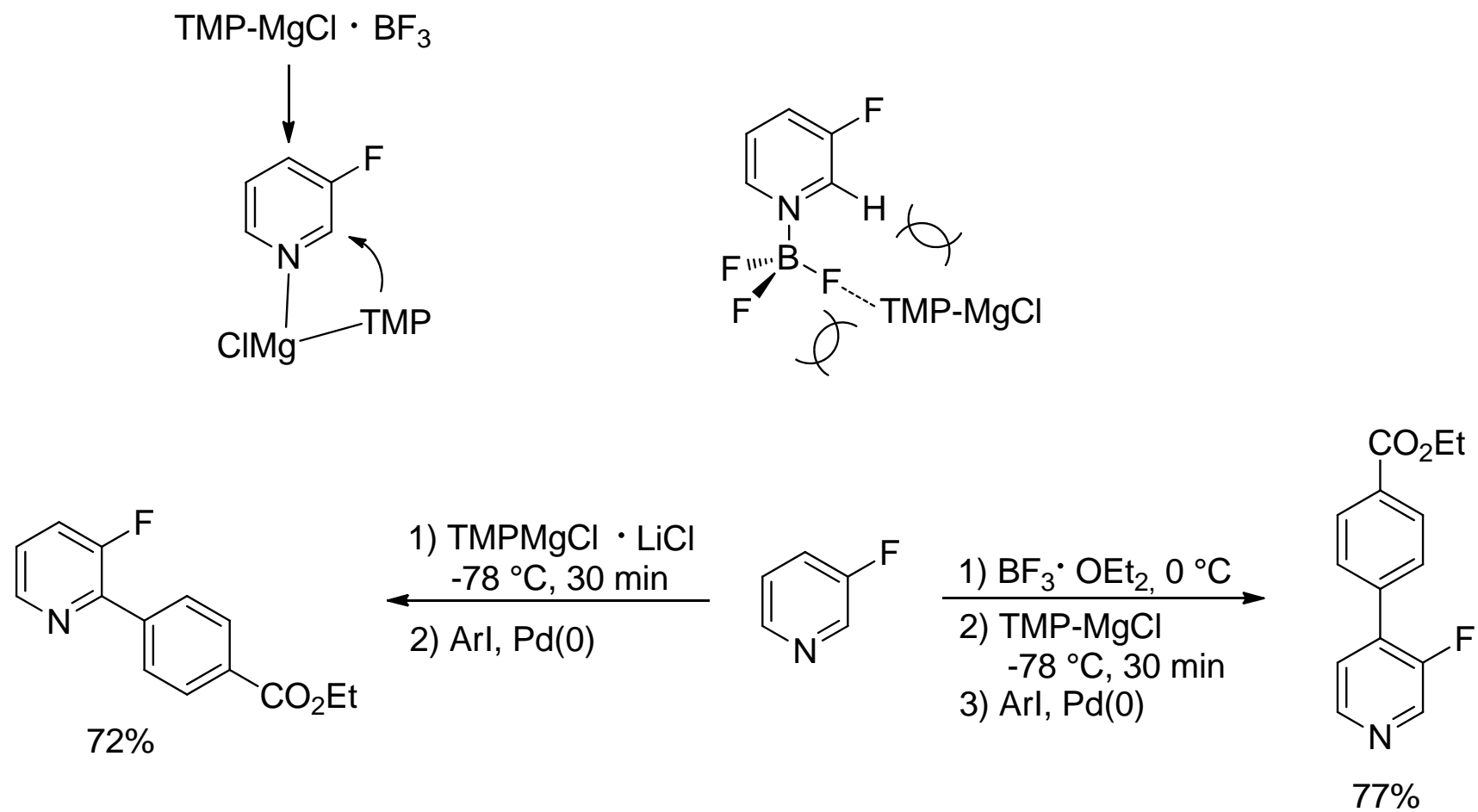


Frustrated Lewis Pairs

B3LYP/6-31G**,def2-SVP

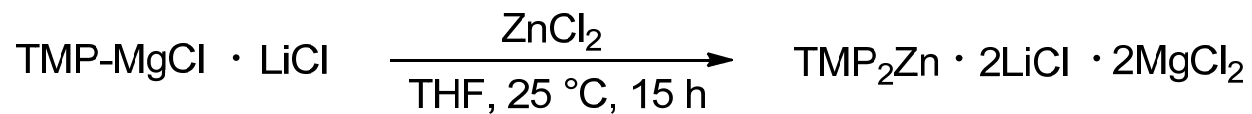


Frustrated Lewis Pairs

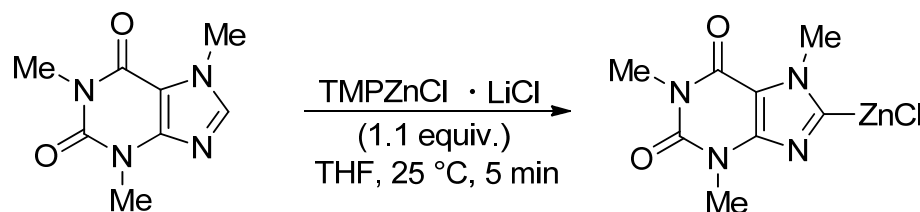
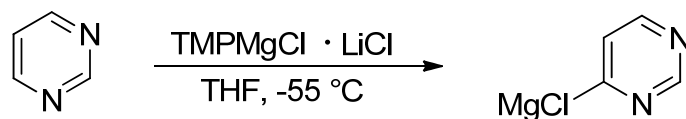
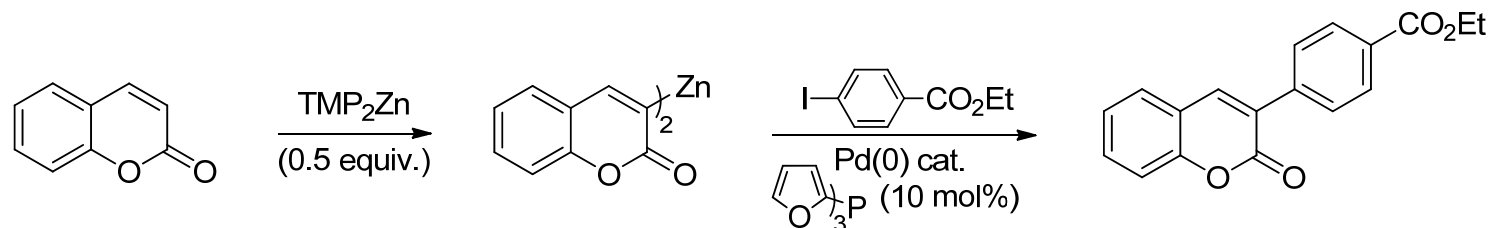


Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.

Metalation



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

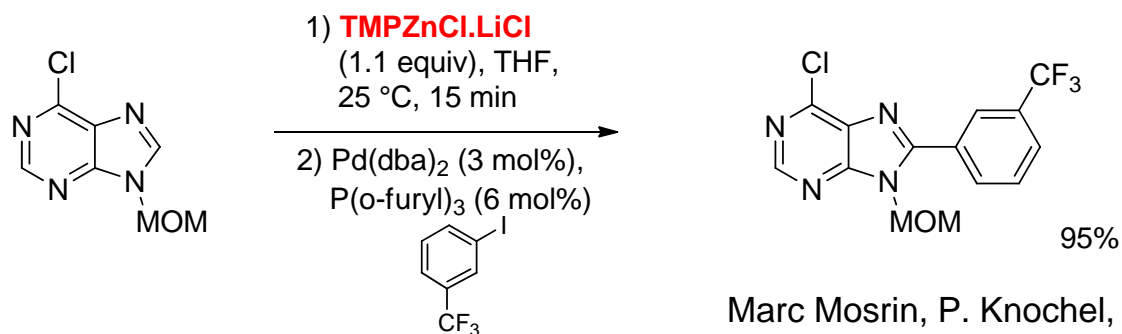
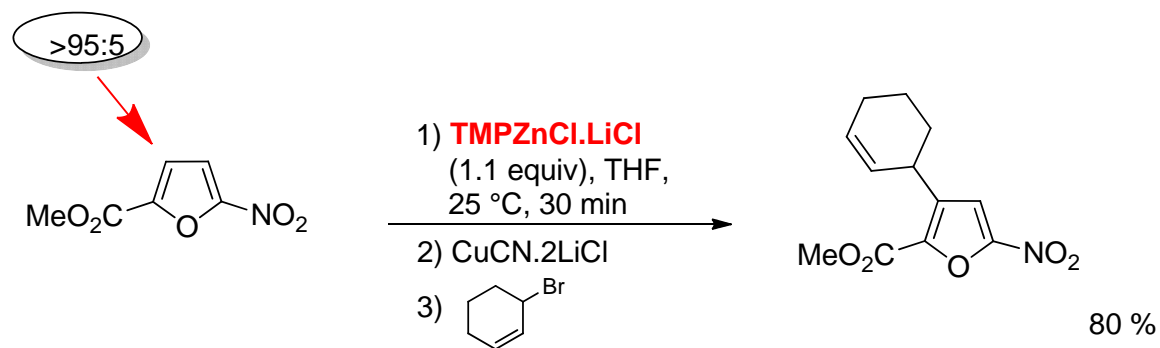


M. Mosrin, P. Knochel *Org. Lett.* **2008**, *10*, 2497

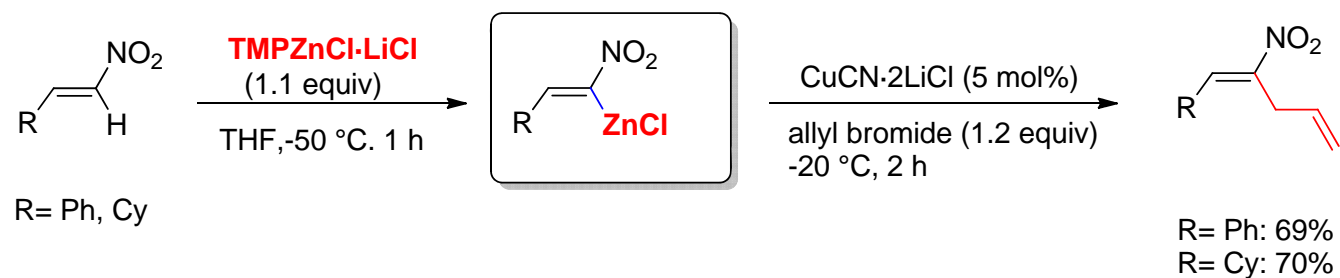
M. Mosrin, P. Knochel *Chem. Eur. J.* **2009**, *15*, 1468

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

Zincations in the presence of ester and nitro groups

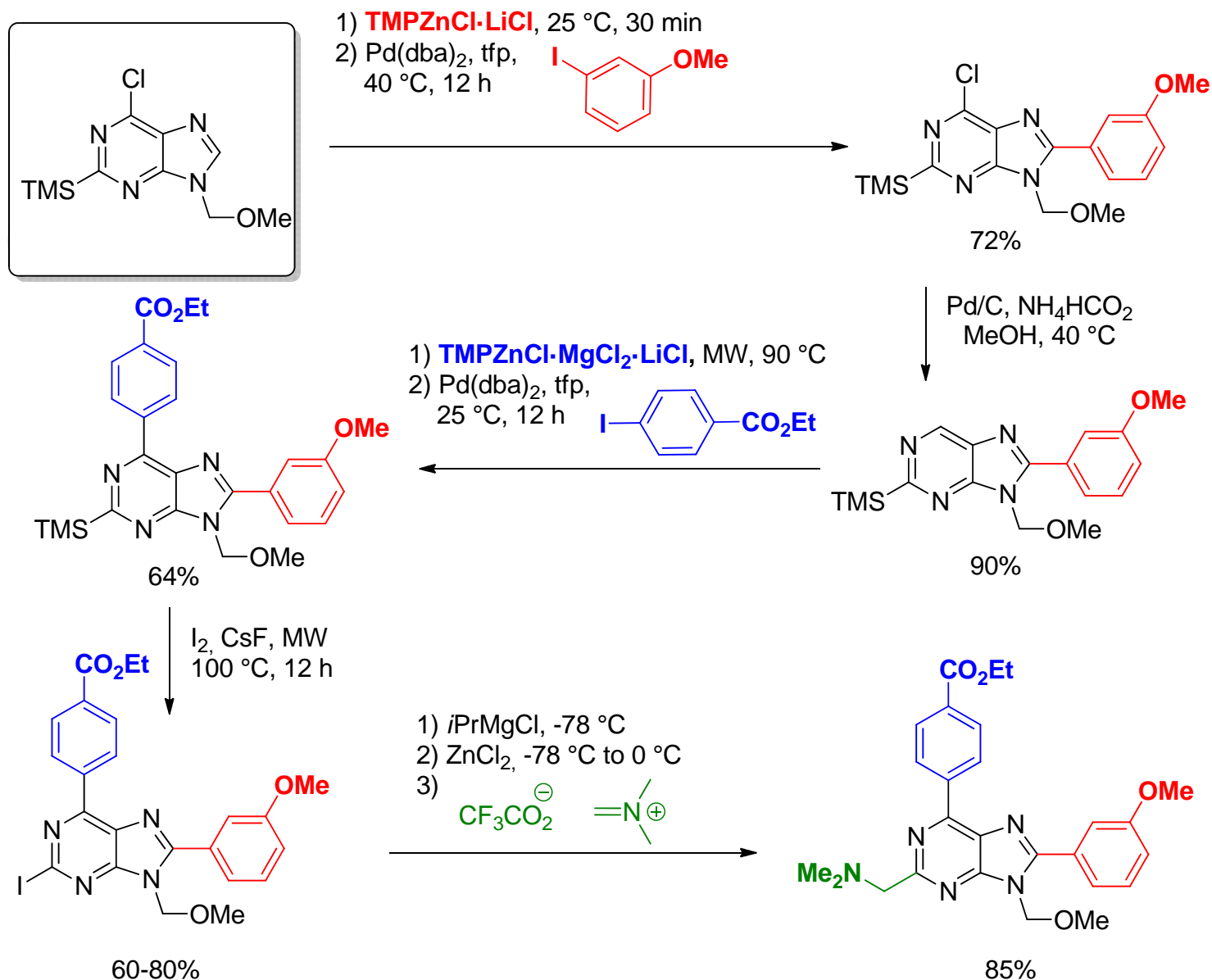


Marc Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837-1840.

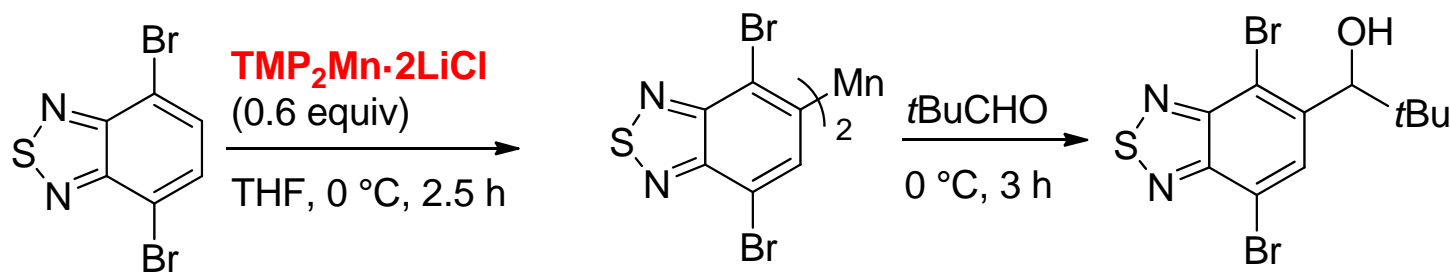


Tomke Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914

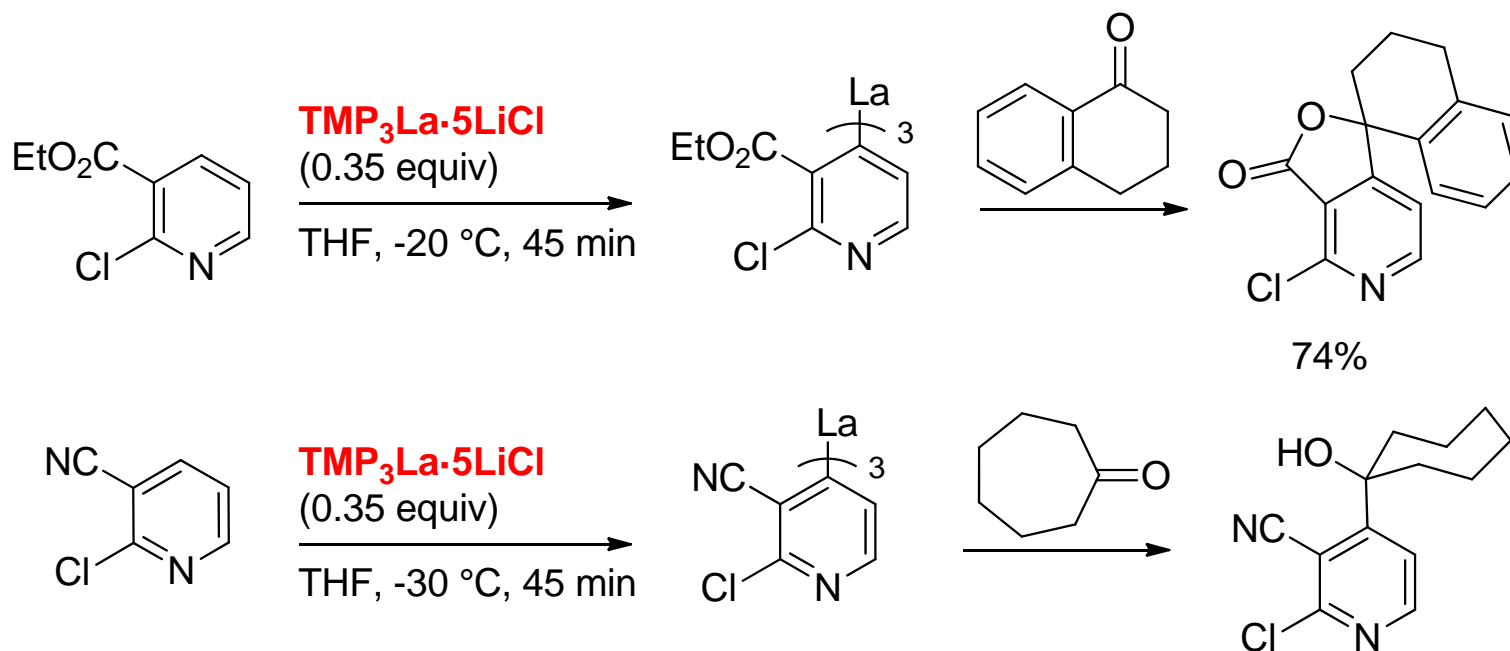
Trifunctionalization of the purine scaffold using Mg and Zn organometallics



Lanthanations and mangnation of heterocycles

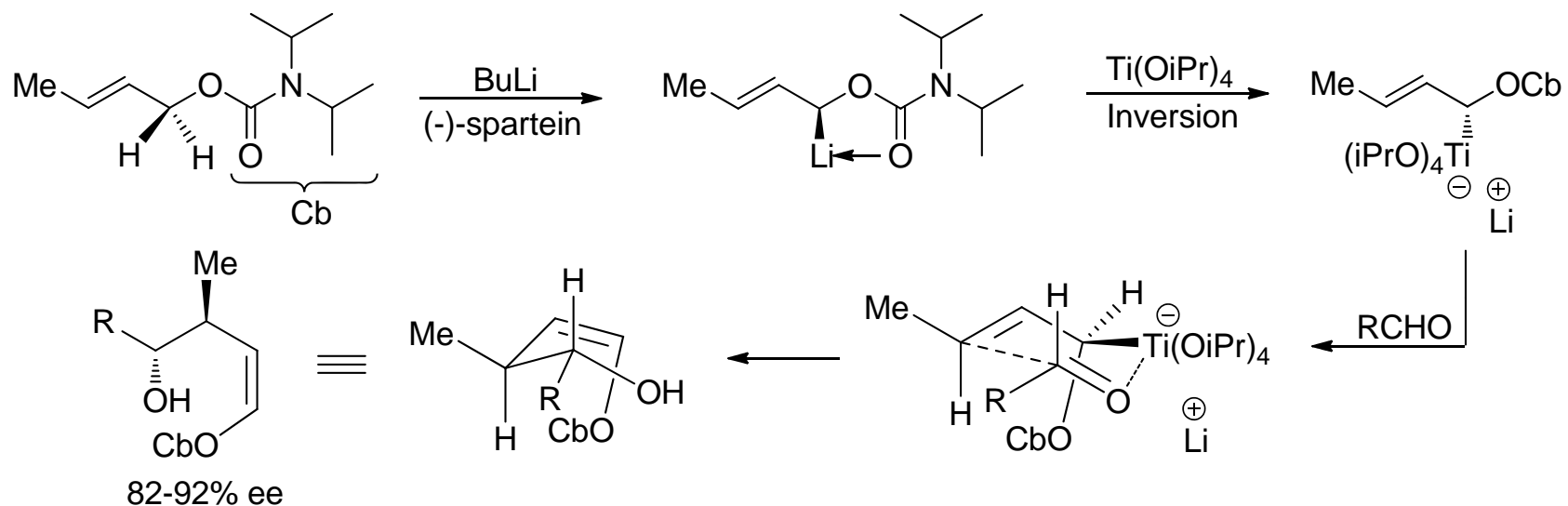


S. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.

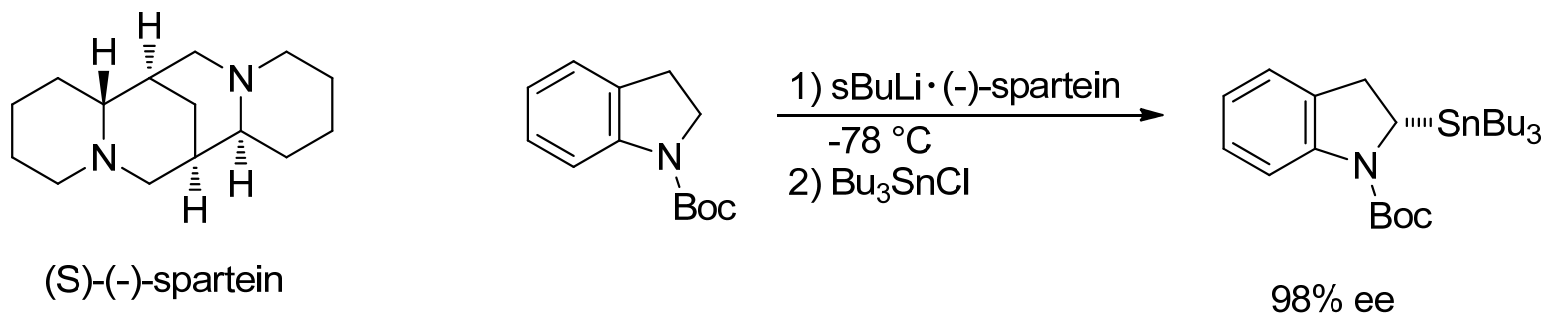


S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 3304-3307.

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

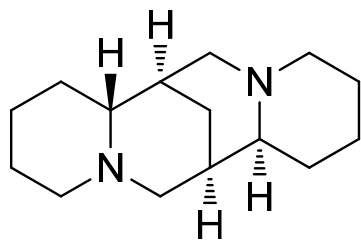
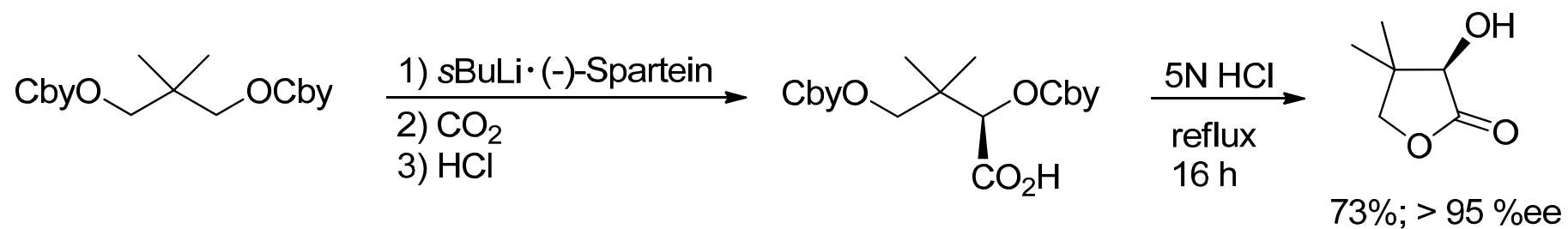


D. Hoppe, et al. *Pure Appl. Chem.* **1994**, 66, 1479.

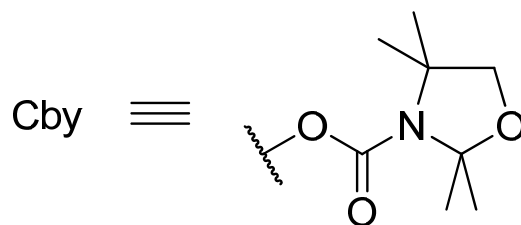


P. Beak *J. Org. Chem.* **1997**, 62, 7679

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

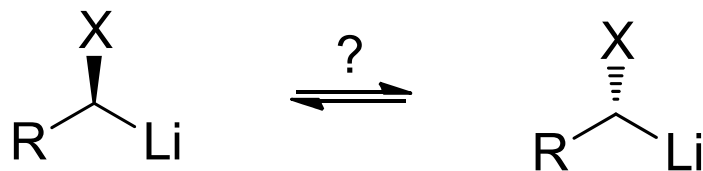


(S)-(-)-Sparteine

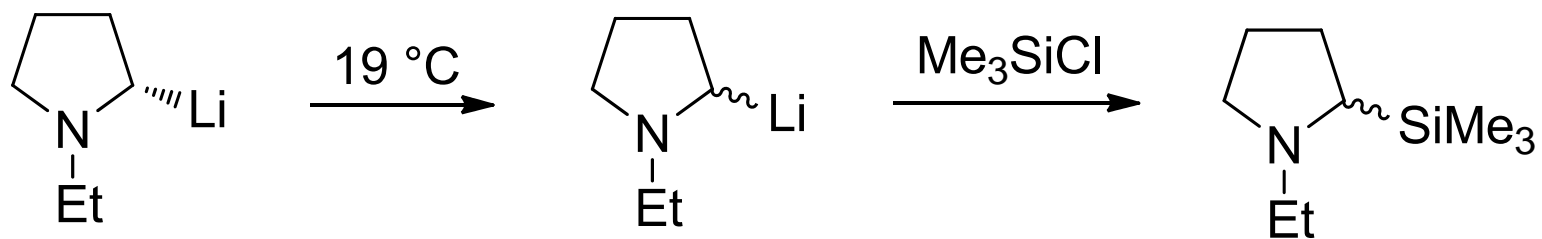


D. Hoppe *Tetrahedron Lett.* **1992**, 33, 5327

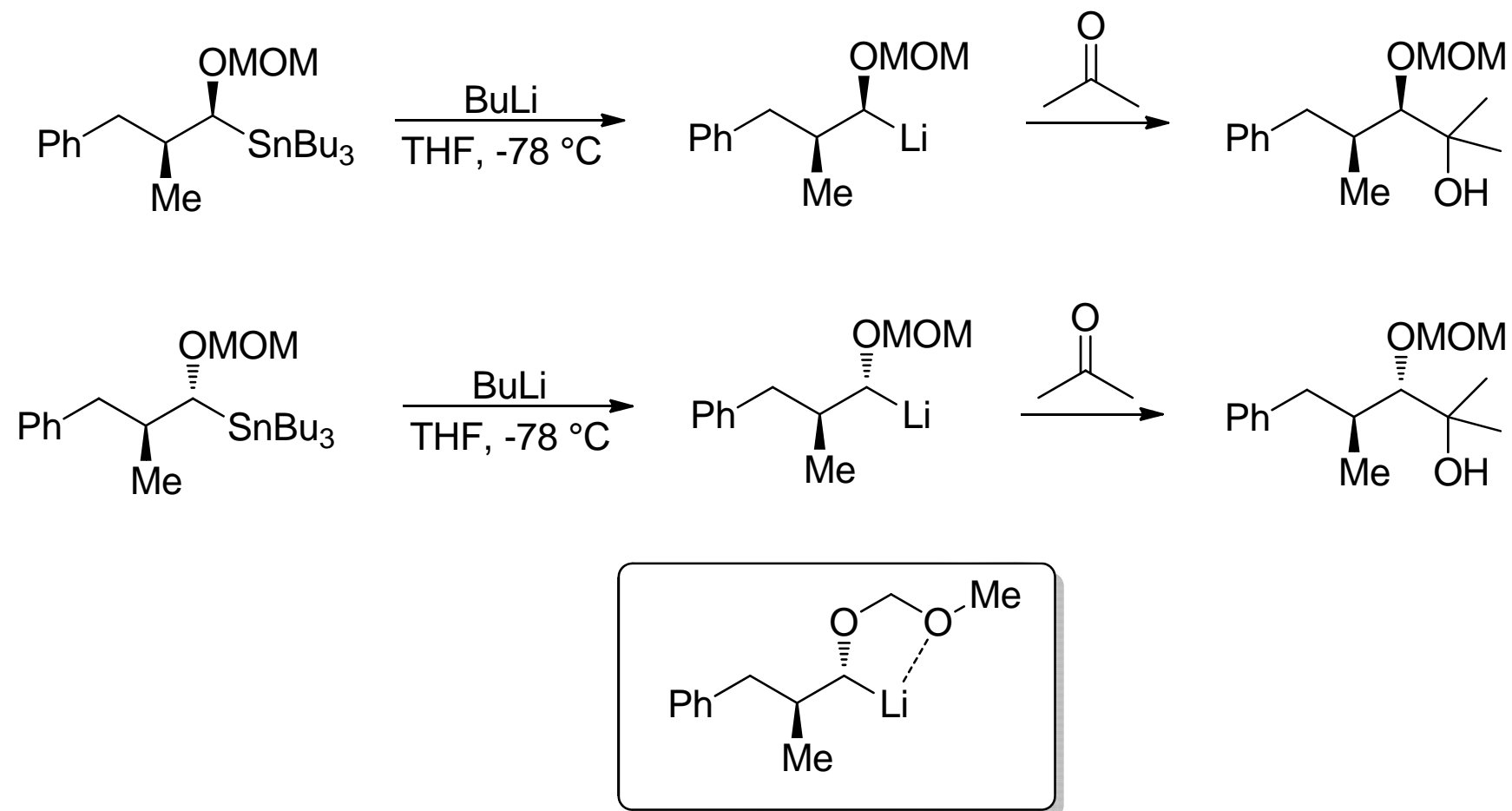
Configurational stability



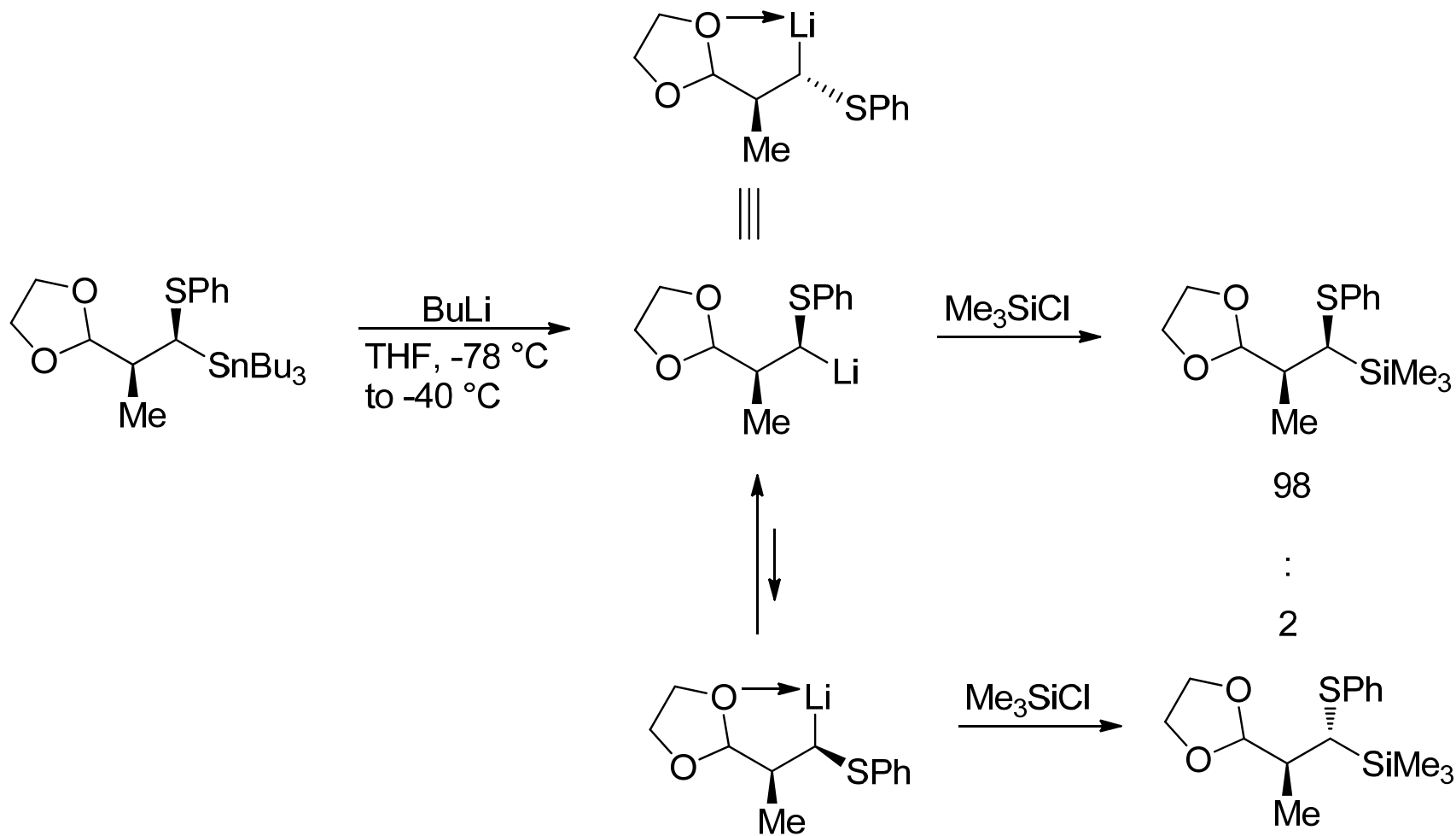
X=Br, SePh, SPh, OCH₂OMe, OCONiPr₂



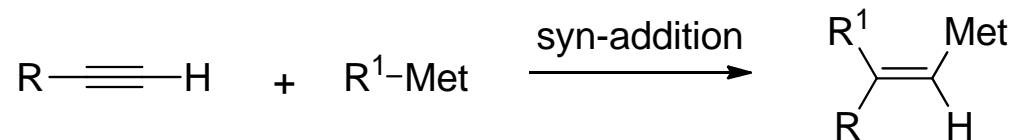
Diastereoselective transmetalation



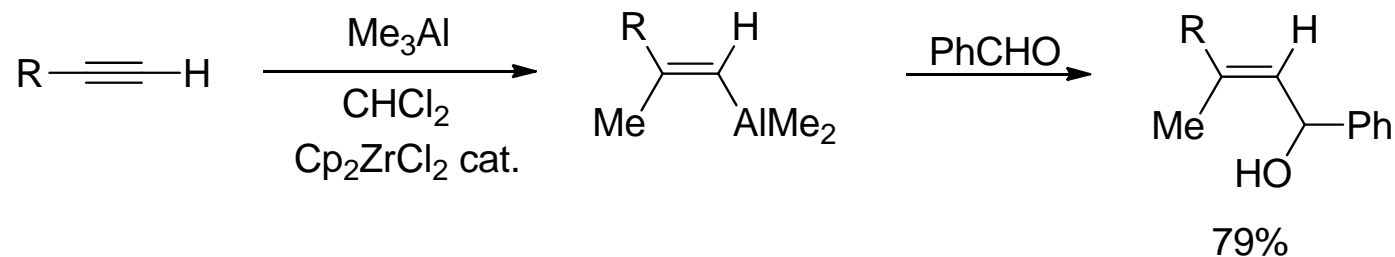
Diastereoselective transmetalation



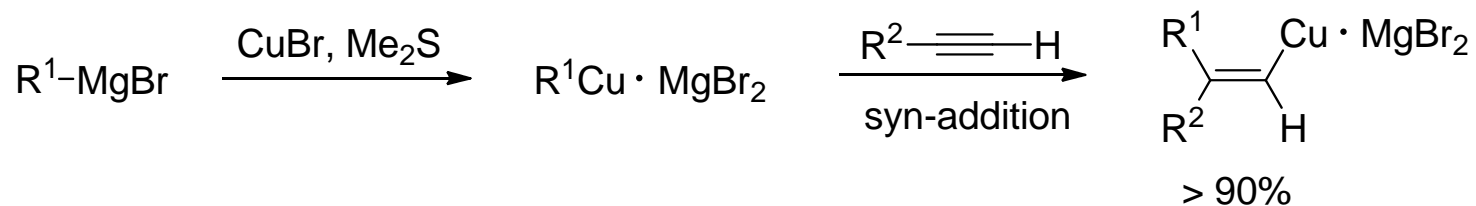
Carbometalation



Negishi-reaction: carboalumination



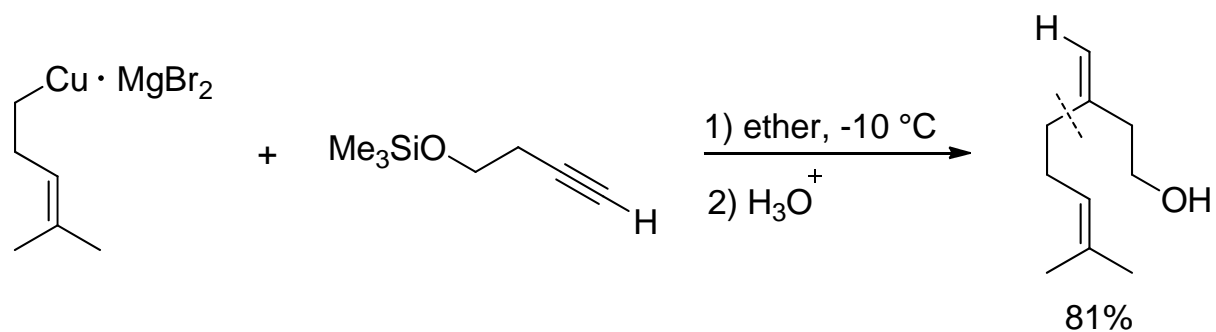
E. Negishi *J. Am. Chem. Soc.* **1976**, 98, 6729



Normant-reaction: carbocupration

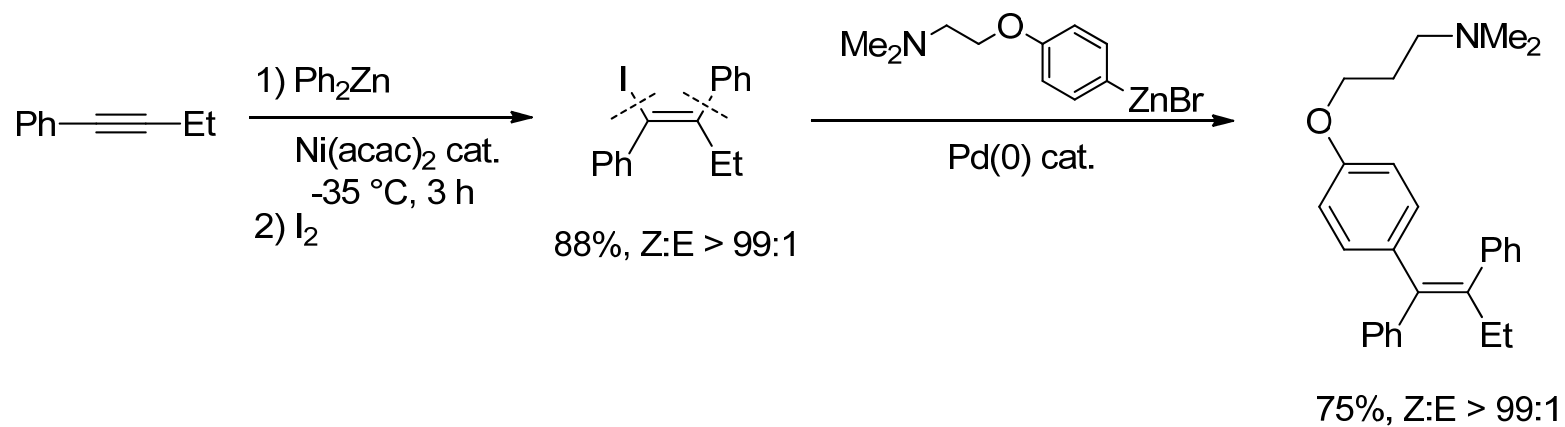
Review: A. Alexakis, J. F. Normant, *Synthesis* **1981**, 841.

Carbometalation



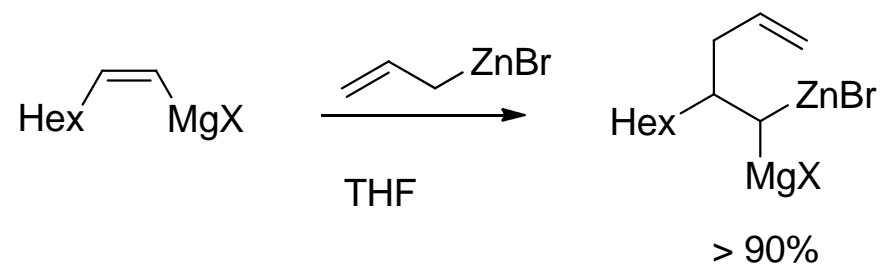
A. Alexakis, J. F. Normant, *J. Organomet. Chem.* **1975**, 96, 471

Tamoxifen-Synthesis: Carbozincation

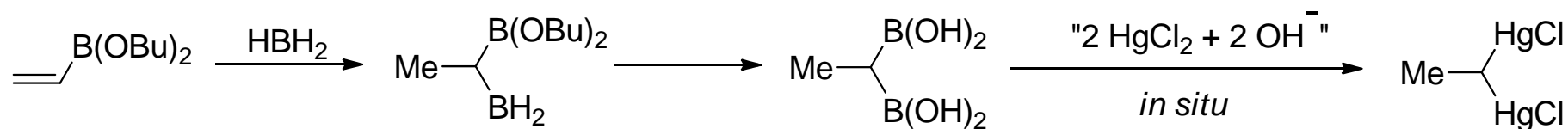


T. Stüdemann, P. Knochel *Angew. Chem.* **1997**, 109, 132

Carbometalation, hydrometalation



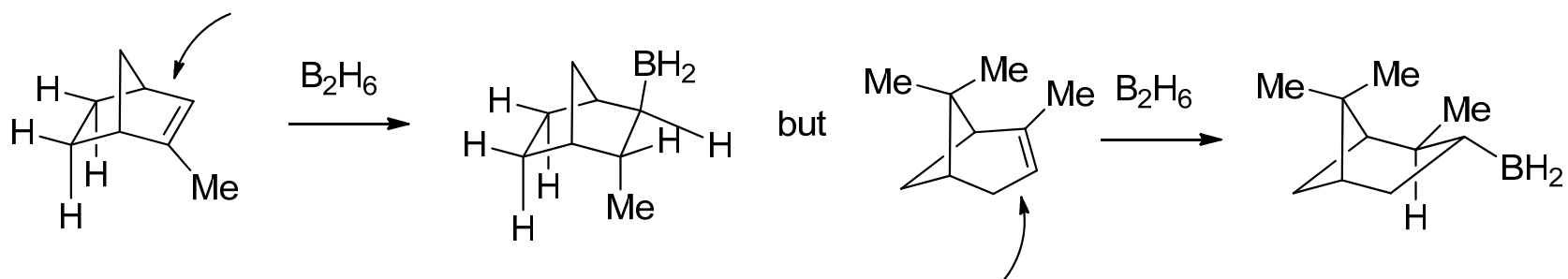
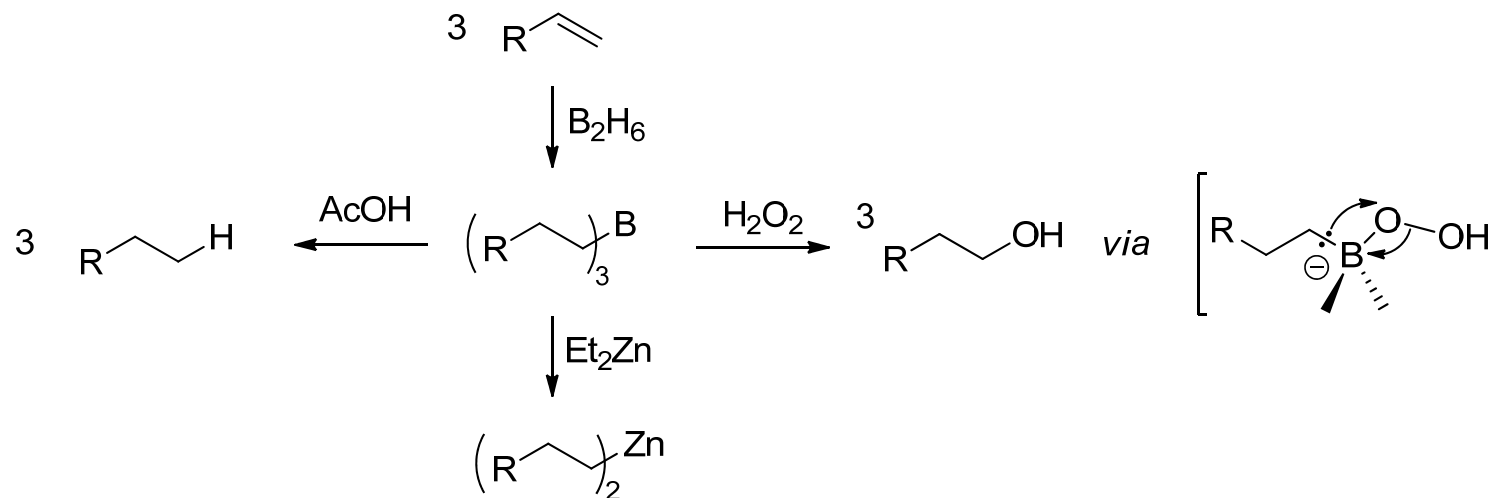
P. Knochel, J. F. Normant *Tetrahedron Lett.* **1986**, 27, 1039; 1043; 4427



D. Matteson, *J. Org. Chem.* **1964**, 29, 2742

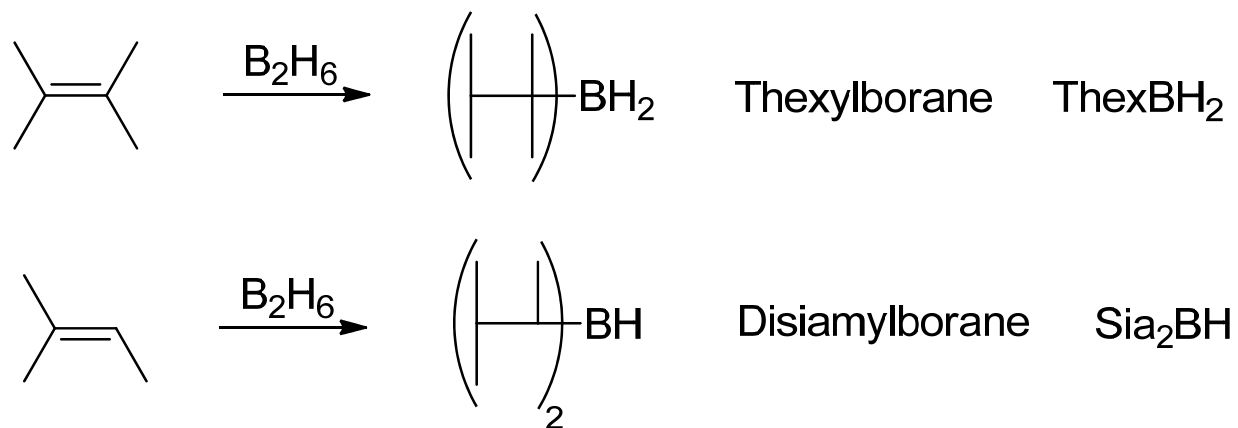
Hydrometalation and application of organoboranes in organic chemistry

hydroboration



Hydroboration

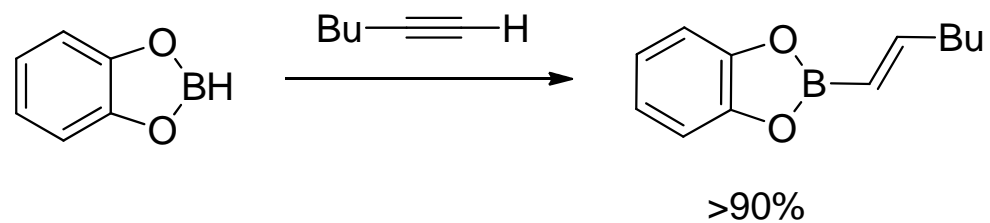
selective hydroborating reagents



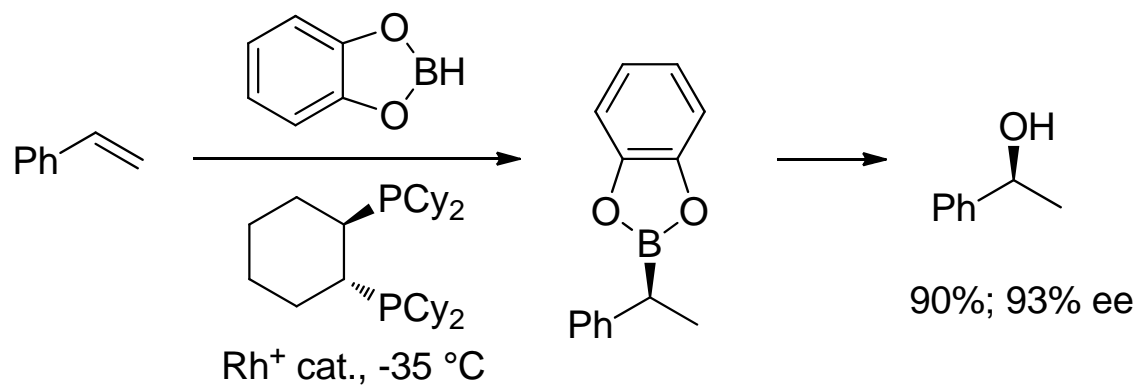
H. C. Brown, E. Negishi *J. Am. Chem. Soc.* **1975**, 97, 2799

Hydroboration

catecholborane



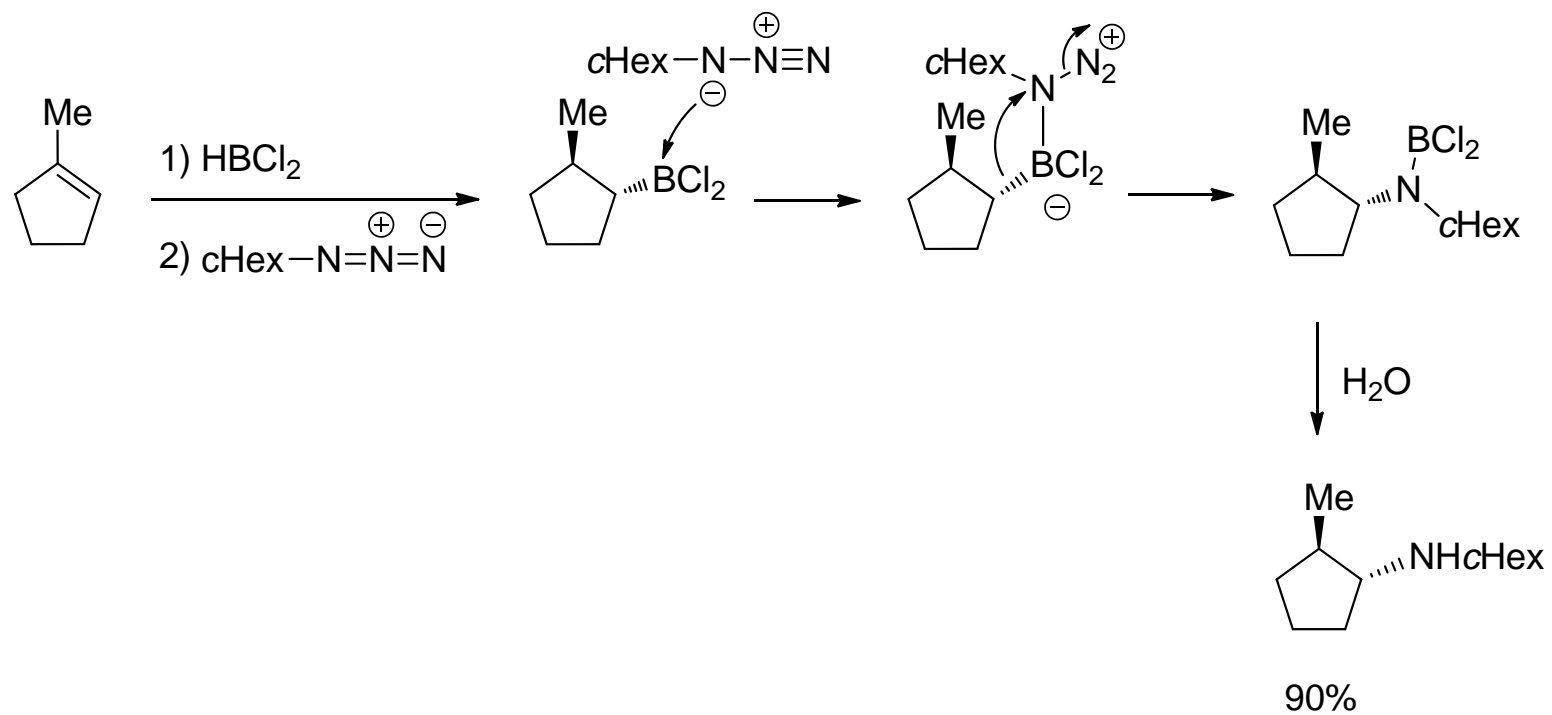
A. Arase, et al., *Synth. Comm.* **1995**, 25, 1957.



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

Hydroboration

amination

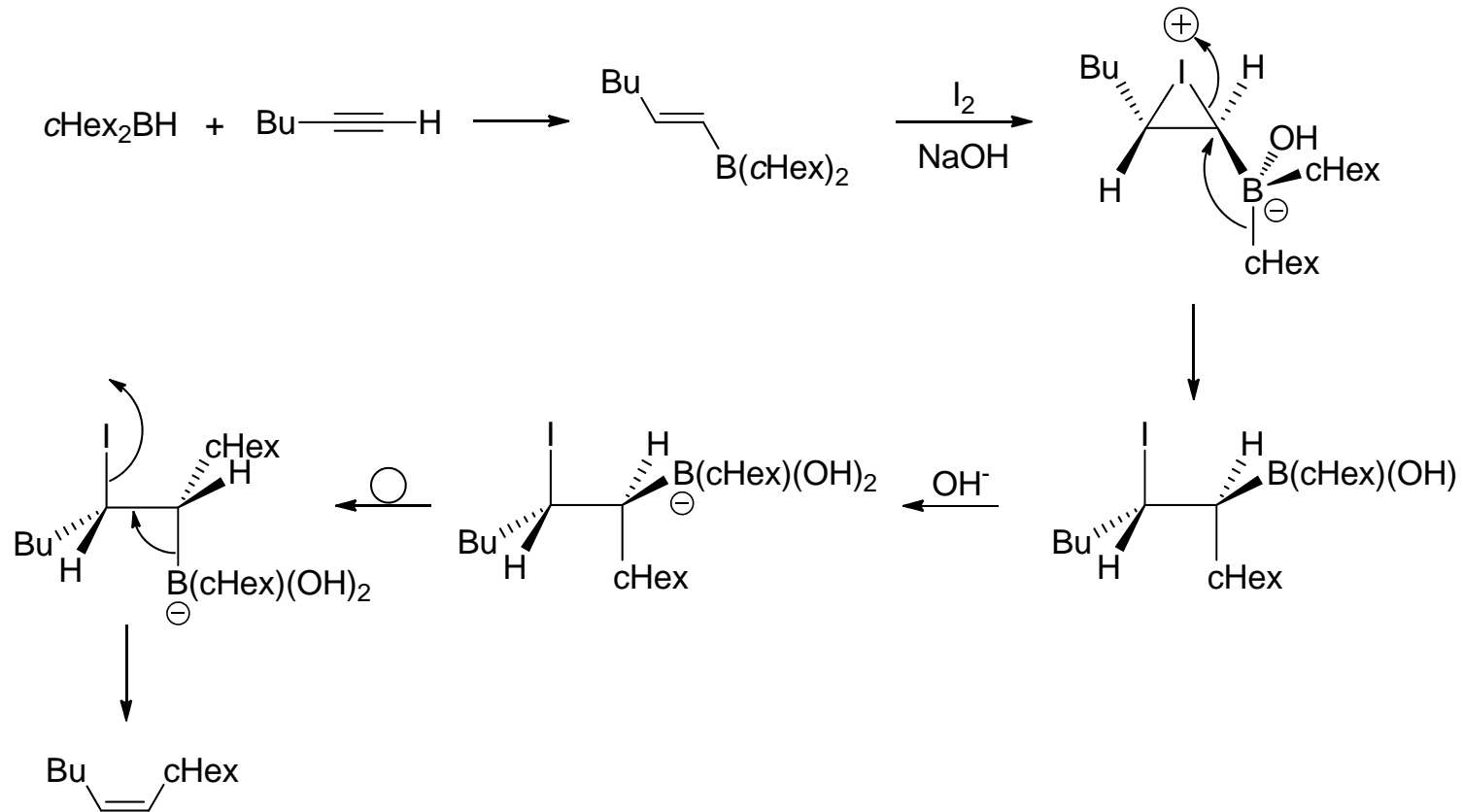


H. C. Brown, et al. *Tetrahedron* **1987**, 43, 4079

Hydroboration

stereoselective synthesis of olefins

Z-olefins

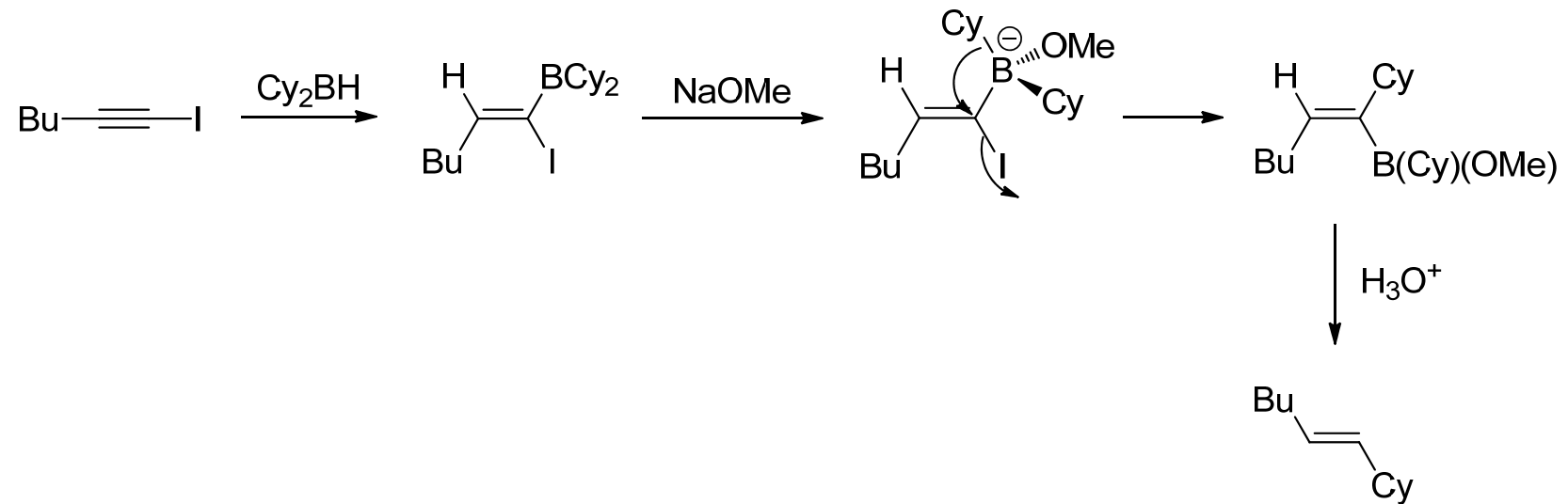


G. Zweifel, et al. *J. Am. Chem. Soc.* **1972**, *94*, 6560.

Hydroboration

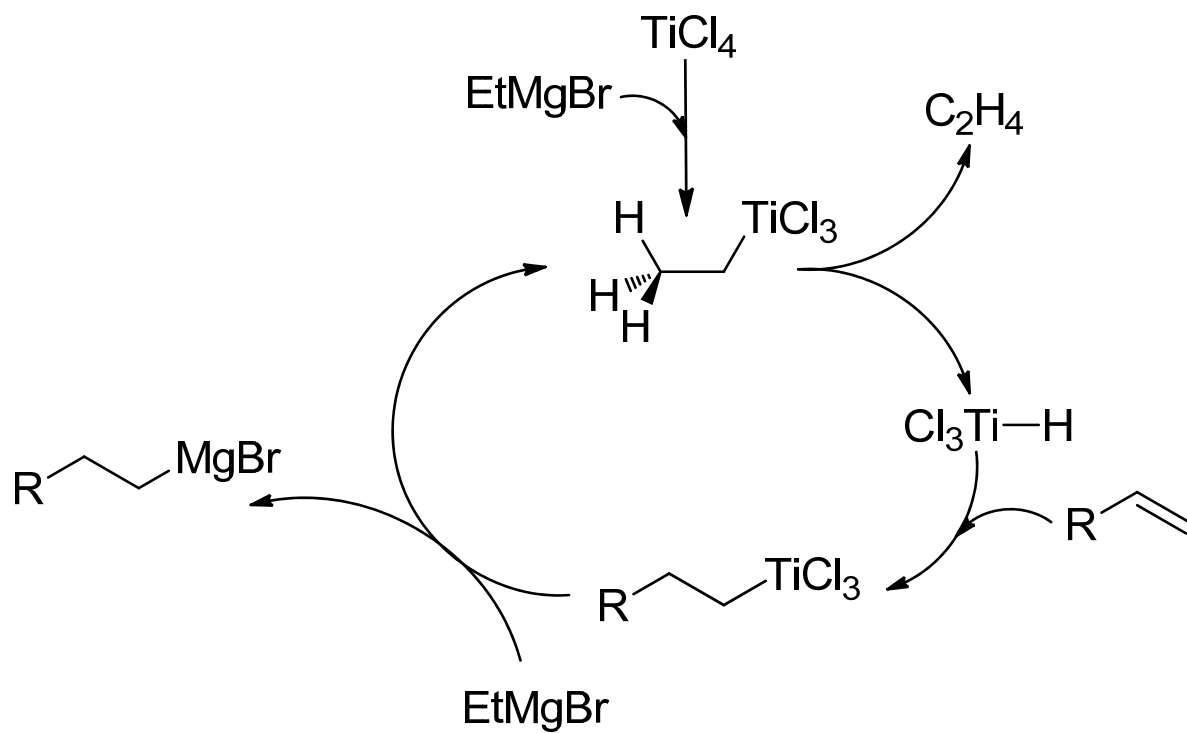
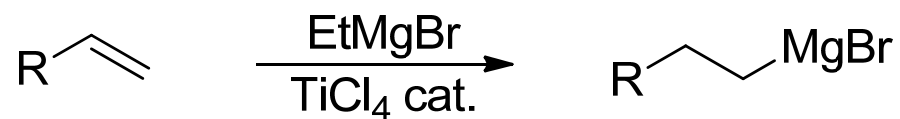
stereoselective synthesis of olefins

E-olefins

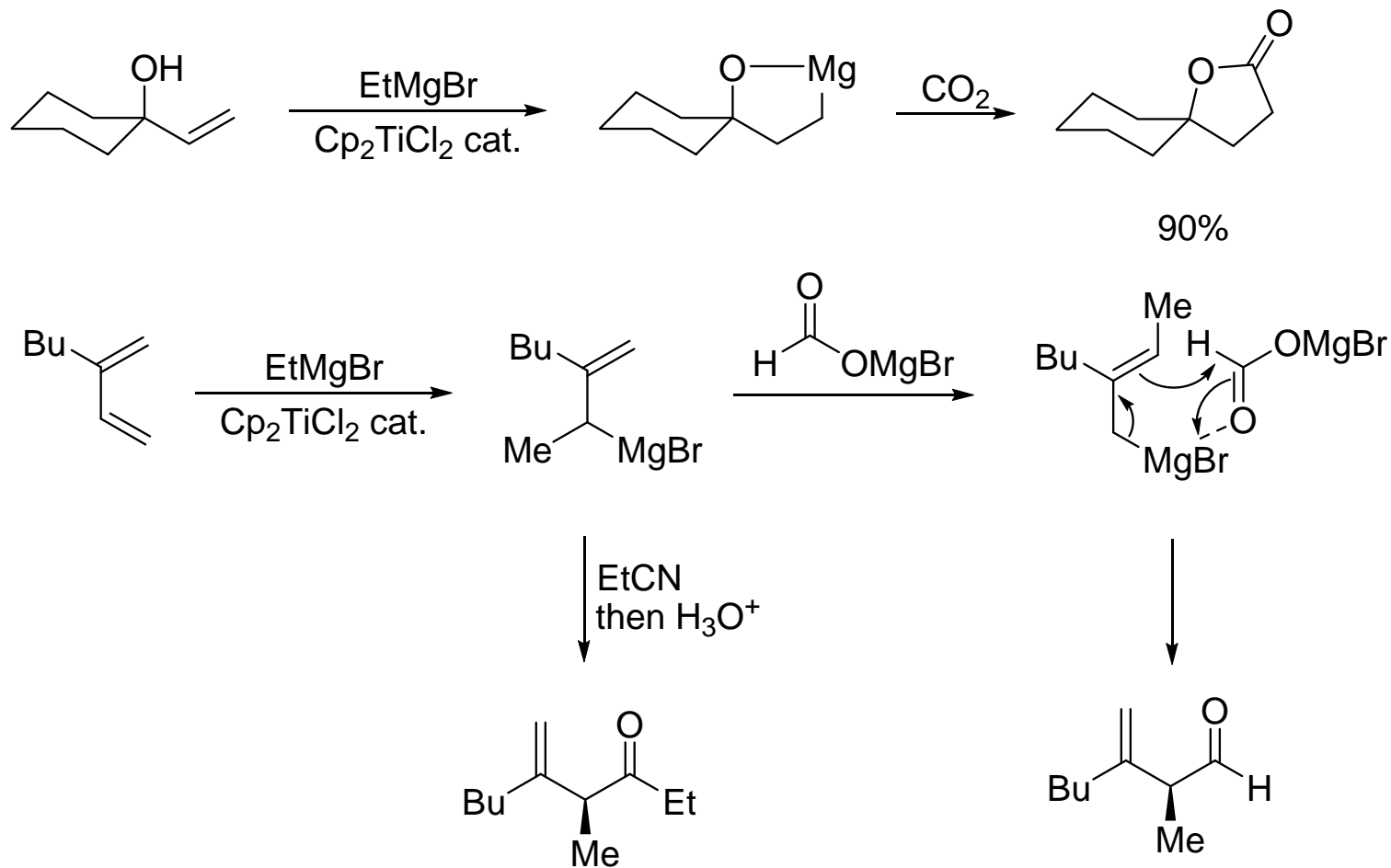


H. C. Brown, et al *J. Org. Chem.* **1989**, 54, 6064.

Hydromagnesiation



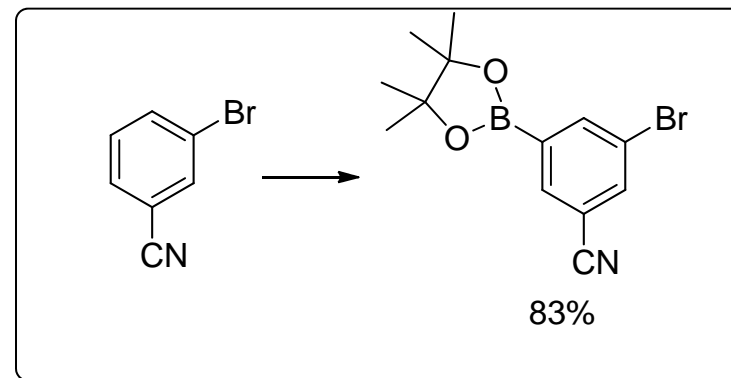
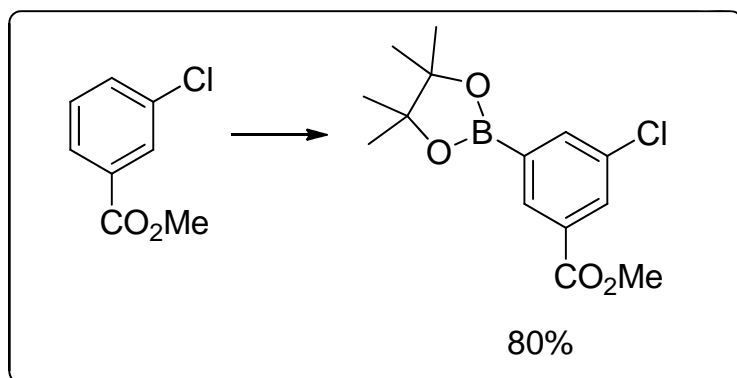
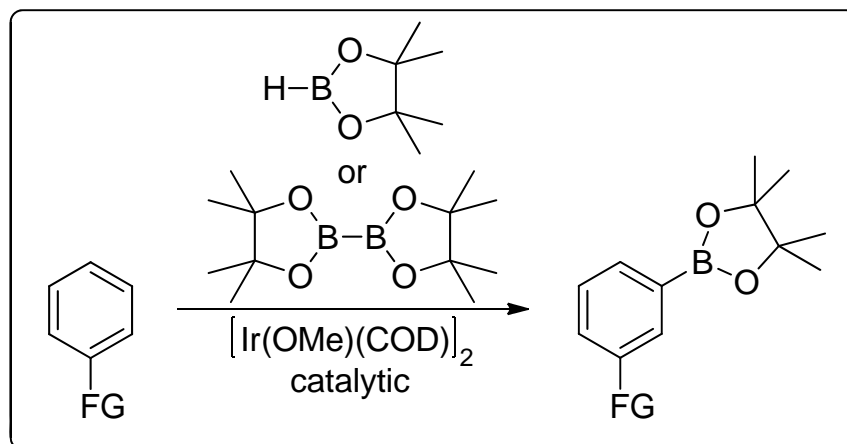
Hydromagnesiation



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

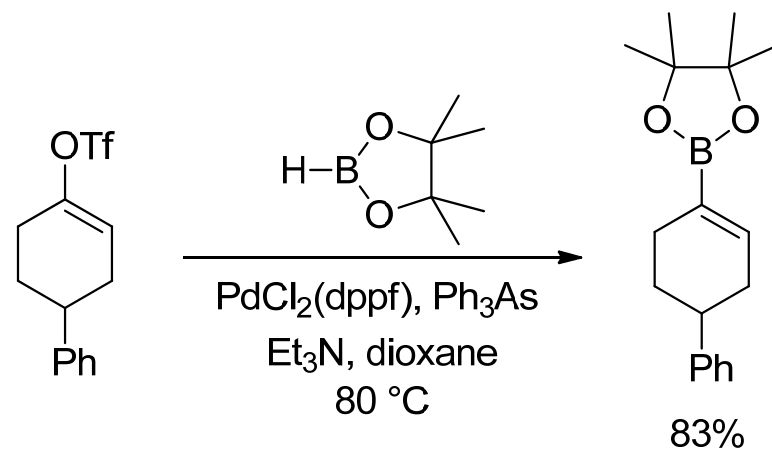
Synthesis of aryl boronic acids

transition-metal catalyzed synthesis of aryl boronic acids



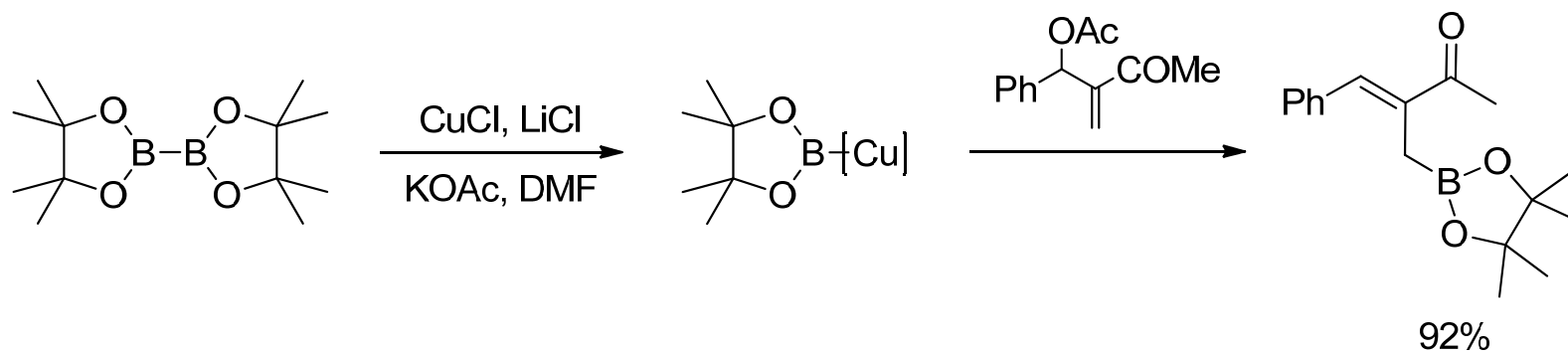
J. F. Hartwig, N. Miyaura, *Chem. Comm.* **2003**, 2924;
J. Am. Chem. Soc. **2002**, 124, 390; *Angew. Chem. Int. Ed.* **2002**, 45, 3056

Synthesis of aryl boronic acids



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

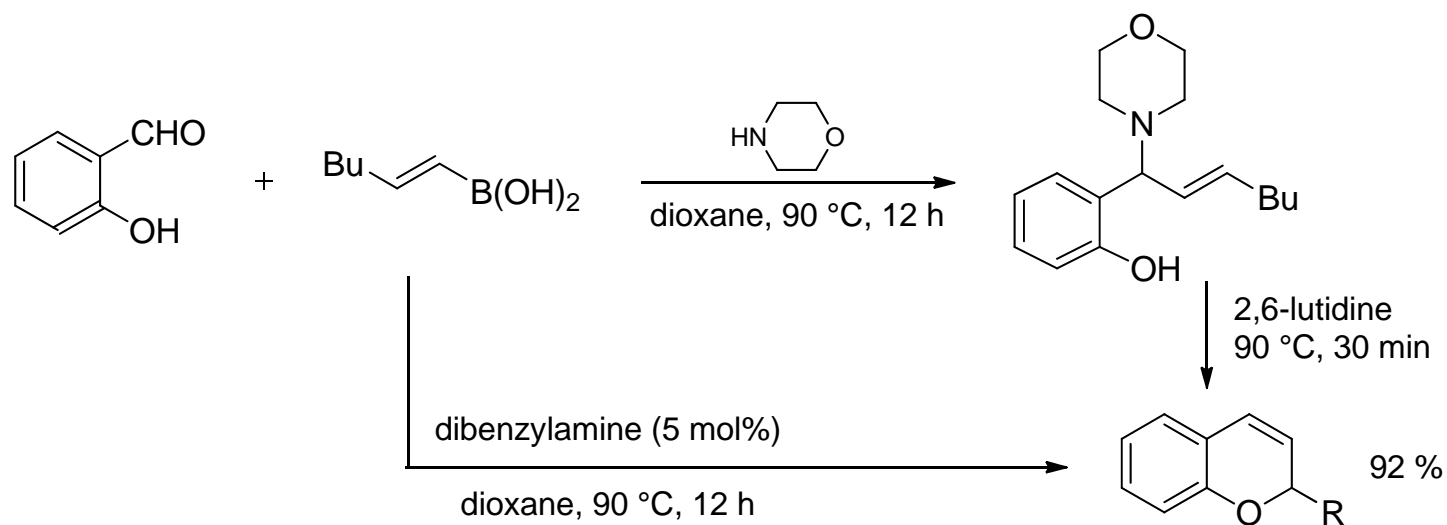
M. Murata *Synth. Comm.* **2002**, 32, 2513



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

Reactivity of unsaturated boronic derivatives

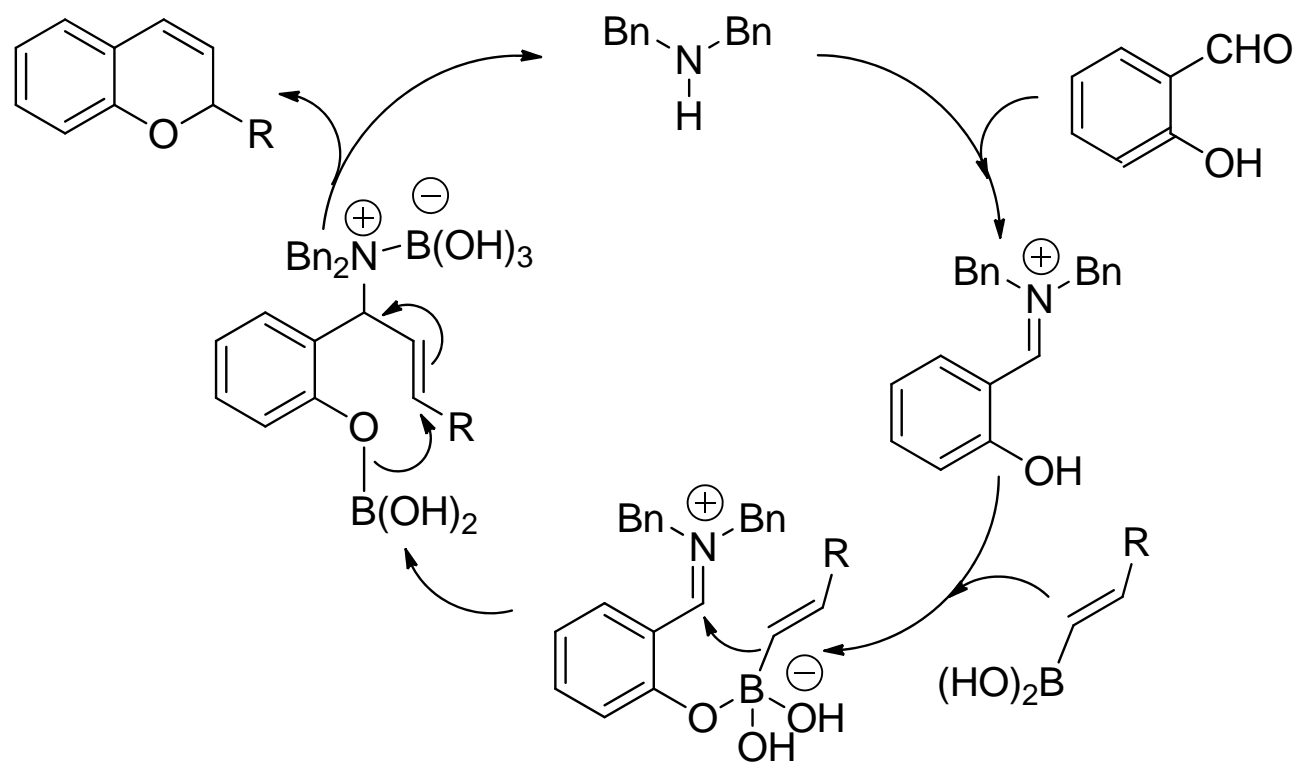
the Petasis-reaction - a short synthesis to 2H-chromenes



Reactivity of unsaturated boronic derivatives

The Petasis-reaction

mechanism

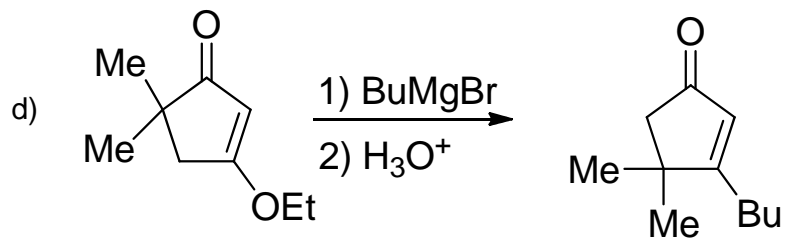
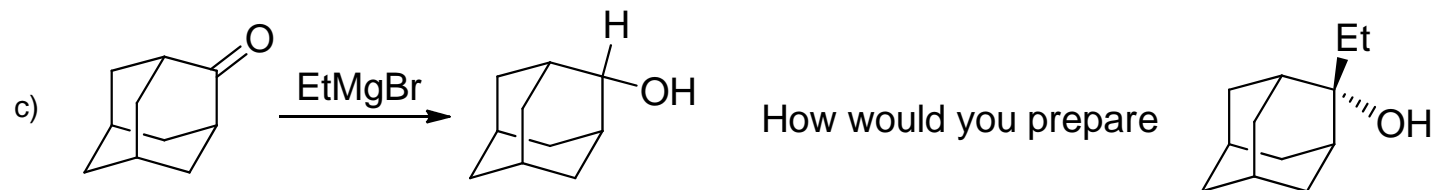
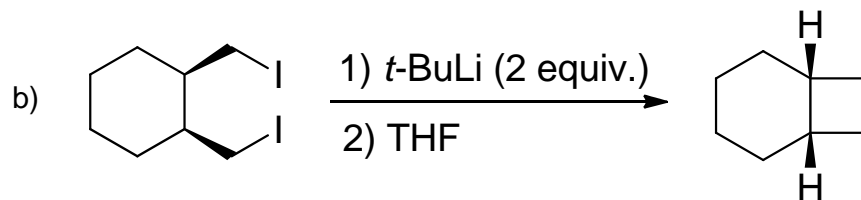
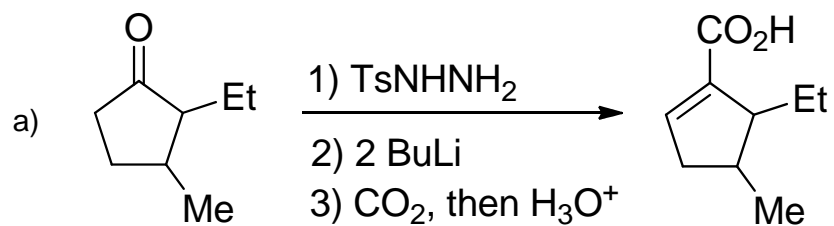


ÜBUNG

1. Problem set

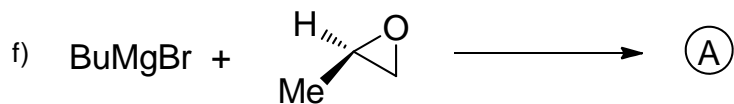
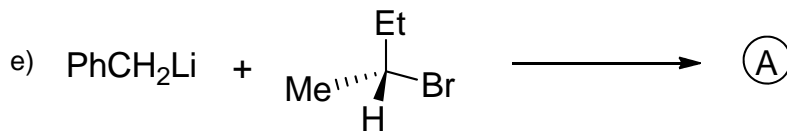
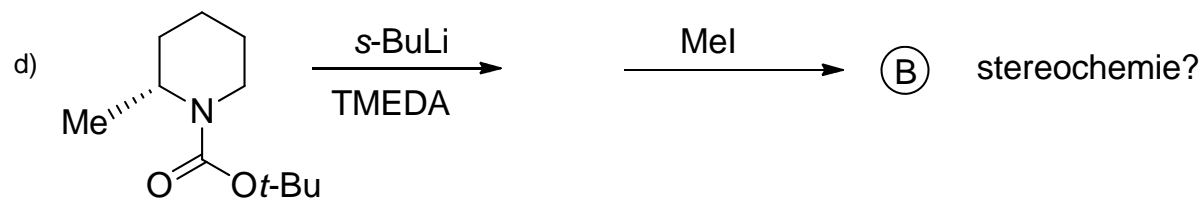
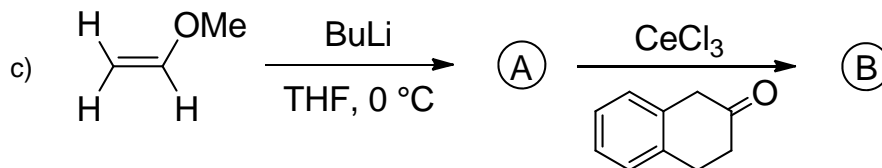
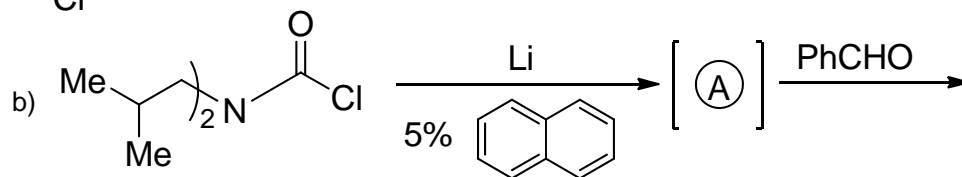
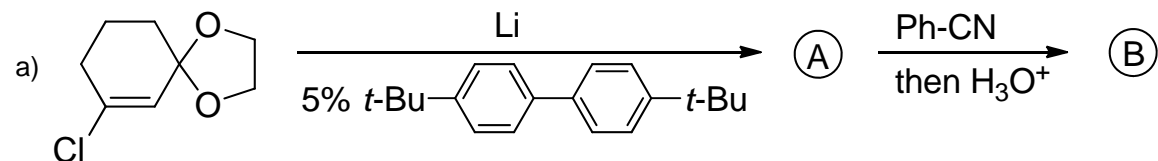
First Problem Set for OC IV

1) Give a mechanism for the following reactions:

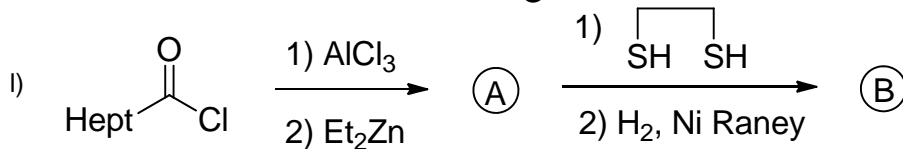
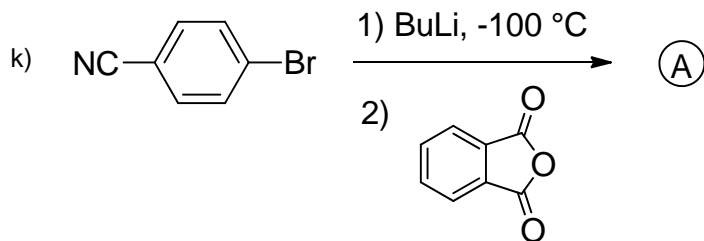
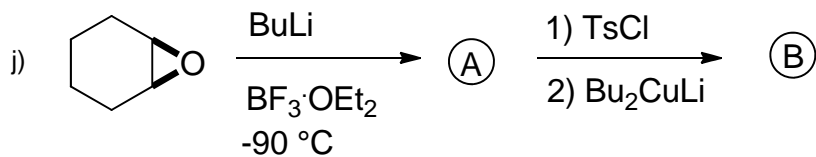
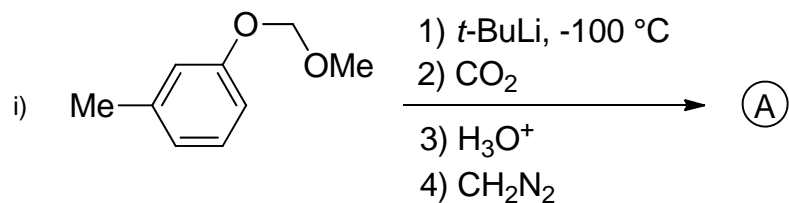
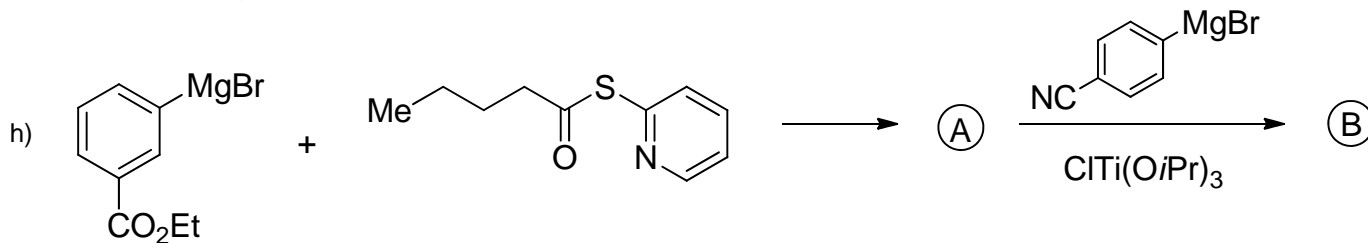
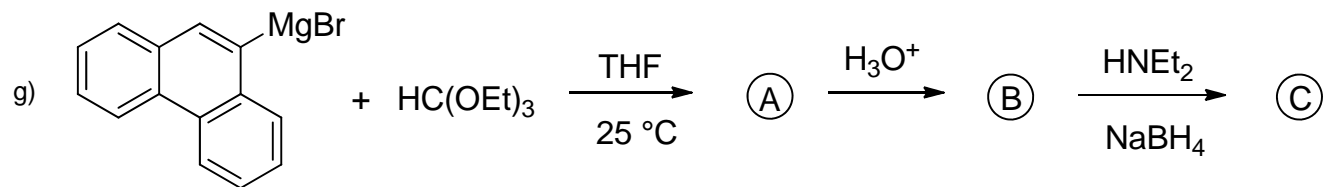


First Problem Set for OC IV

2) Give the following reaction products:

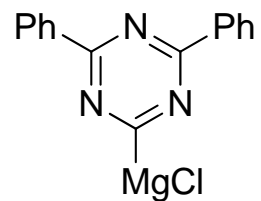
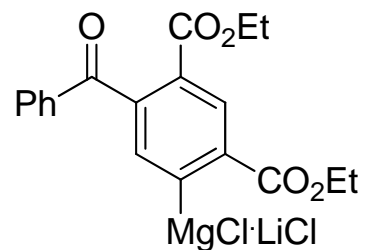
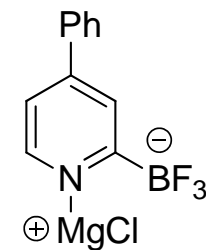
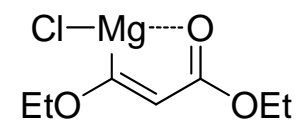
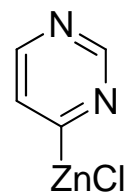
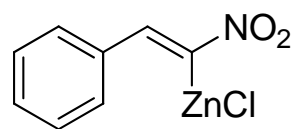
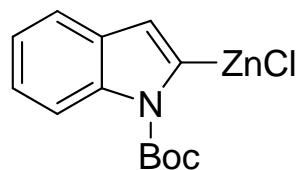
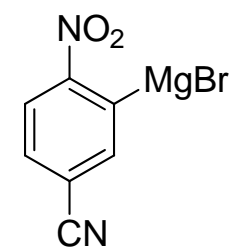
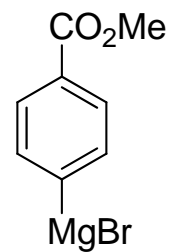
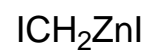
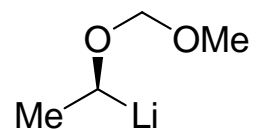
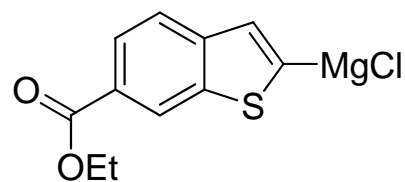


First Problem Set for OC IV

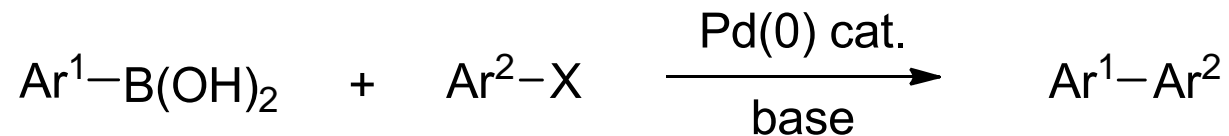


First Problem Set for OC IV

3. How you would prepare following organometallics:



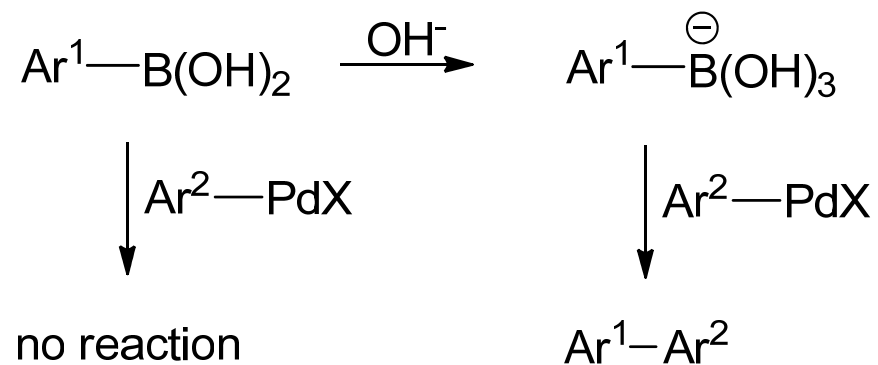
The Suzuki cross-coupling reaction



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

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

Key step

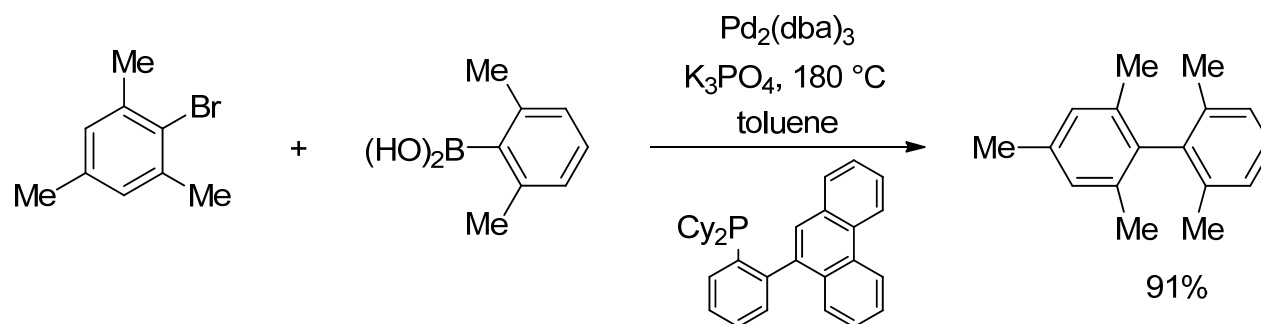


S. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162

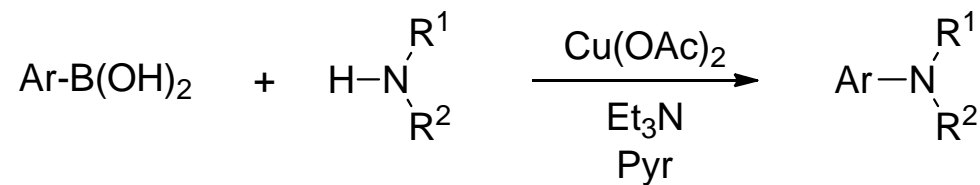
C. Amatore, A. Jutand, G. Le Duc *Chem. Eur. J.* **2011**, *17*, 2492

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

The Suzuki cross-coupling reaction



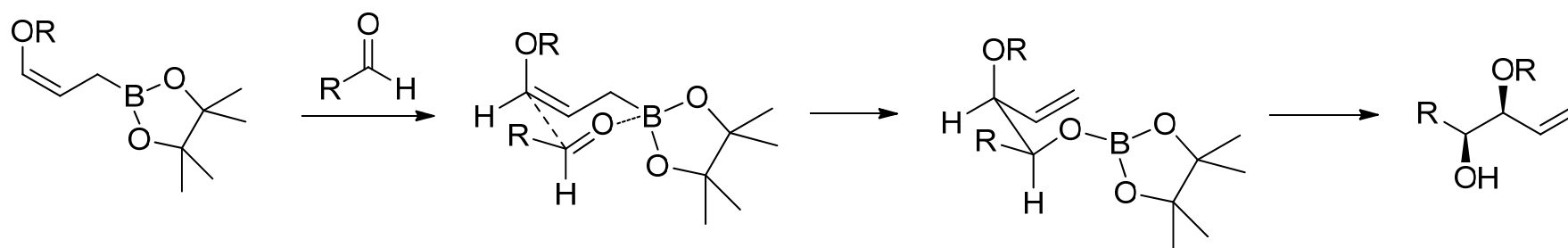
R. E. Sammelson, M. J. Kurth, *Chem. Rev.* **2001**, 101, 137



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

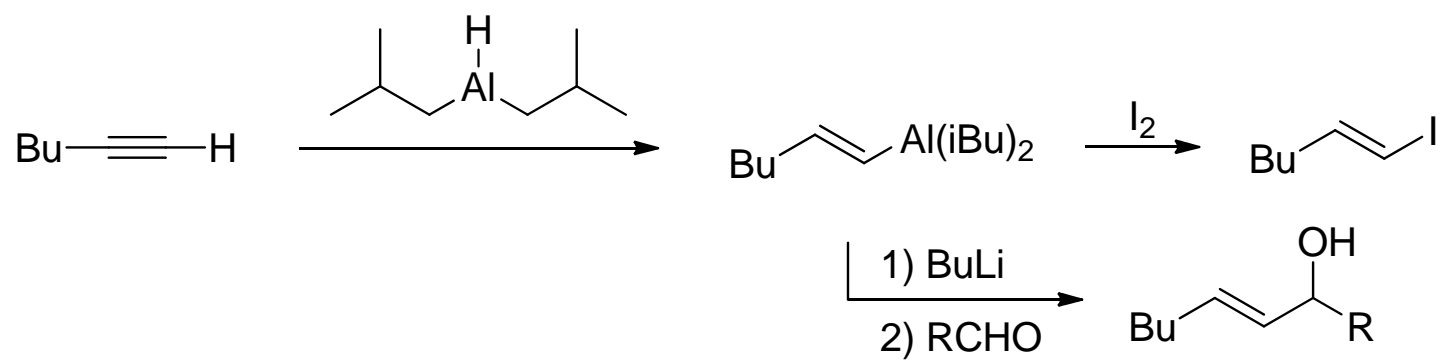
S. Ley, *Angew. Chem. Int. Ed.* **2003**, 42, 5400

Chemistry of allyl boranes



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

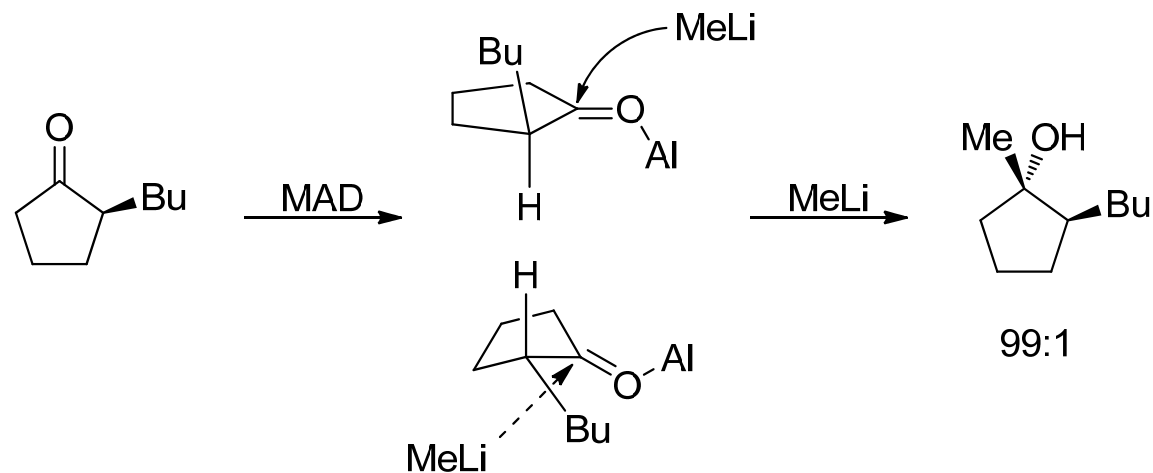
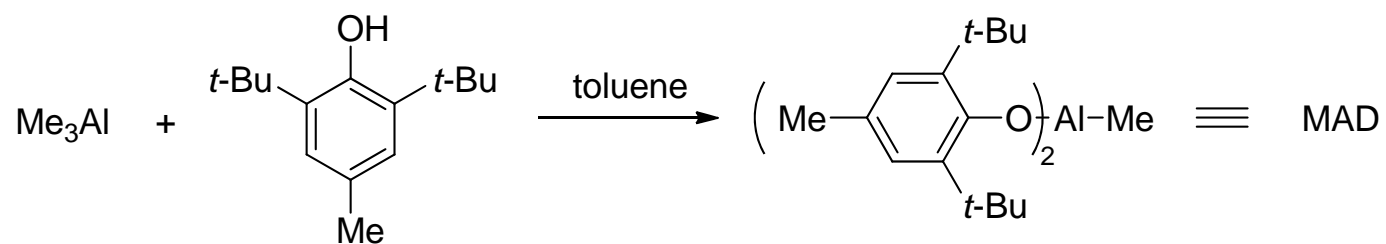
Hydroalumination



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

Hydroalumination

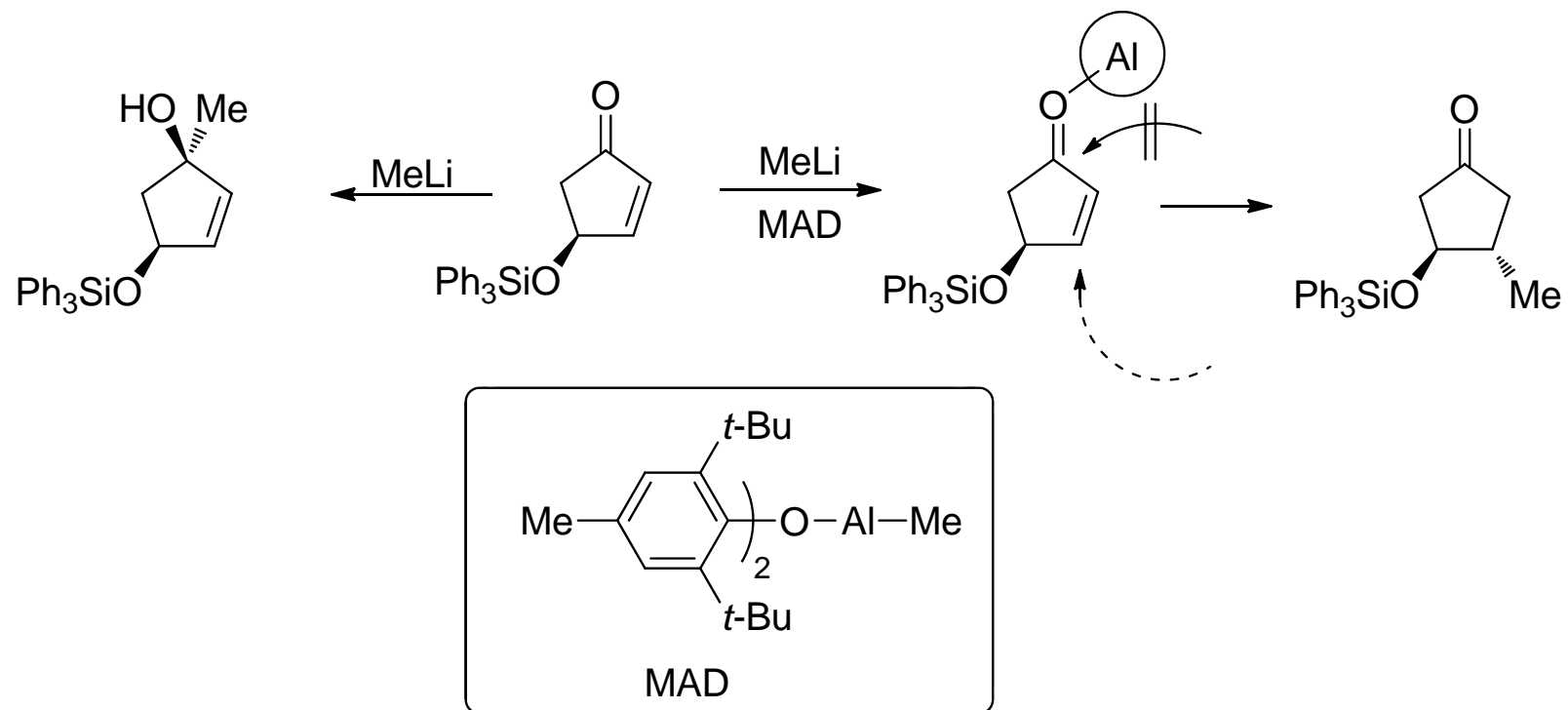
Special Al-reagents



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

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

Hydroalumination

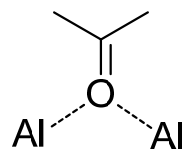


K. Maruoka, H. Yamamoto, *Kagaku, Zokan* (Kyoto, Japan) **1988**, 115, 127
S. Nagahara, K. Maruoka, H. Yamamoto, *Bull Chem Soc.* **1993**, 66, 3783

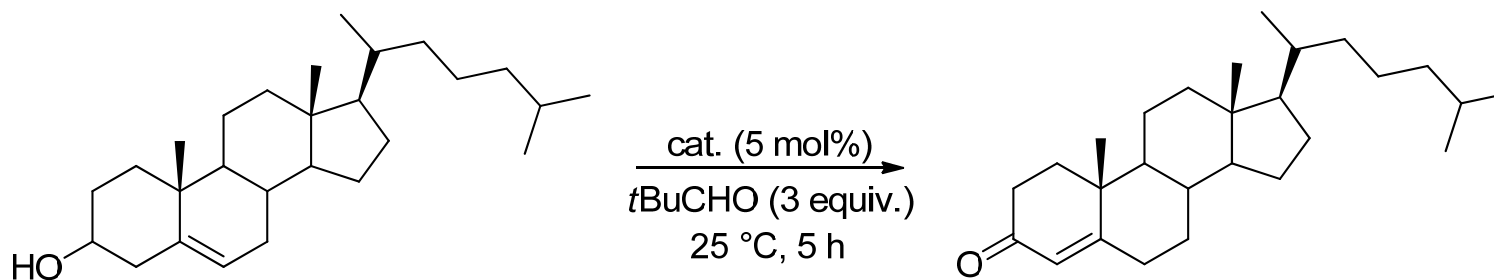
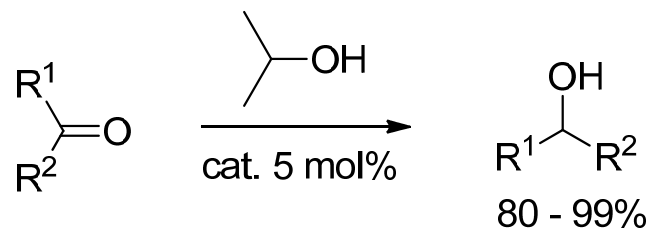
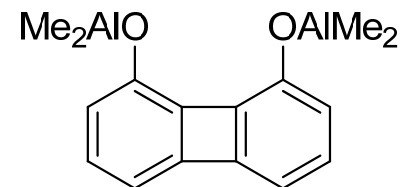
Hydroalumination

Verley-Meerwein-Ponndorf reduction

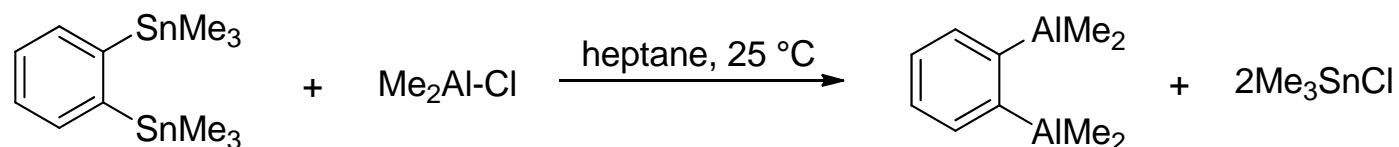
activating a carbonyl group twice



is possible using

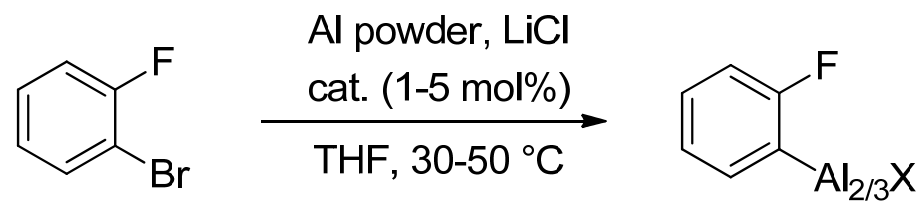


Other preparation of aluminium compounds



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

Direct synthesis of organoaluminium reagents

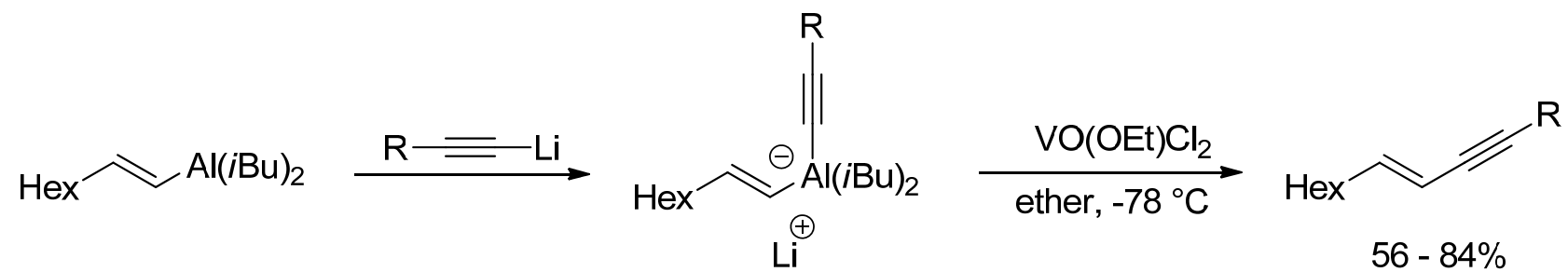


cat. = InCl₃, BiCl₃, PbCl₂, TiCl₄

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

Hydroalumination

Reactivity



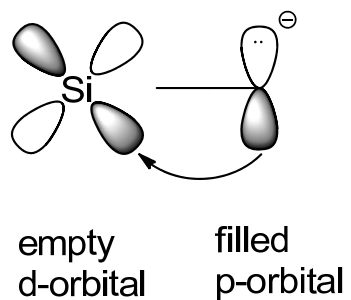
T. Ishikawa, A. Ogawa, T. Hirao *J. Am. Chem. Soc.* **1998**, *120*, 5124

The organic chemistry of main-group organometallics

Silicium

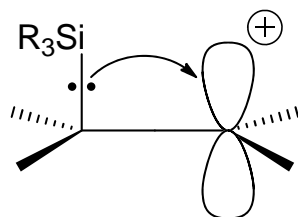
The effect of a Me_3Si -substituent:

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



stabilization of carbanions in α -position

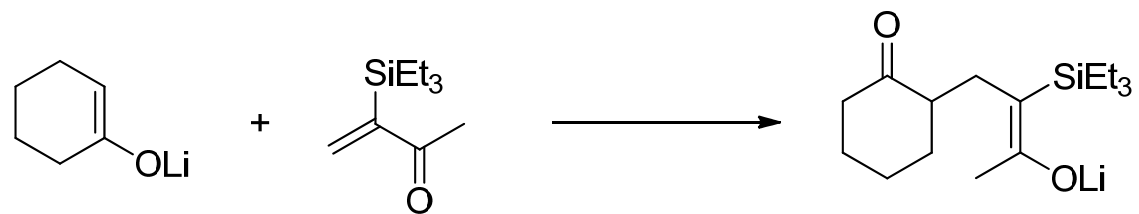
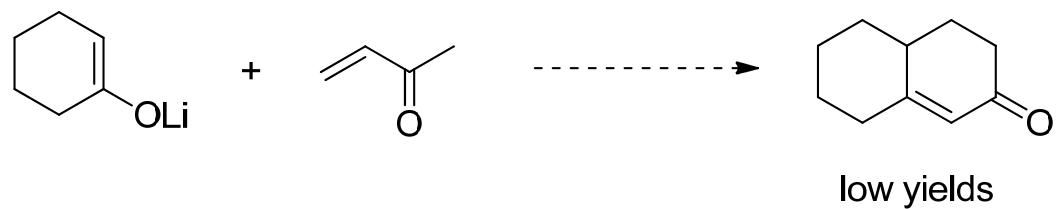
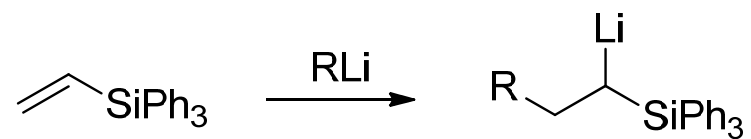
- 3) hyperconjugation: interaction of σ -framework with the π -system



stabilization of a cation in β -position

Silicium

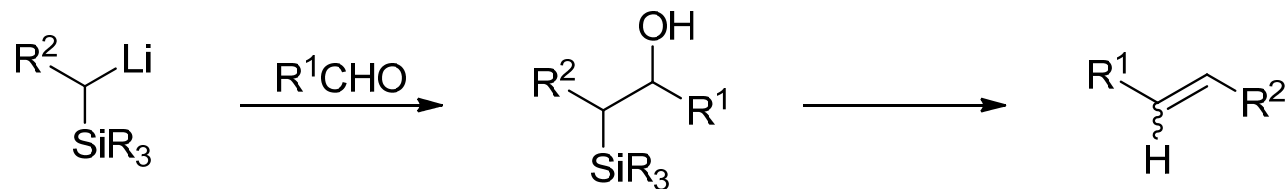
Applications:



high yield: stabilized lithium enolate
(no polymerization)

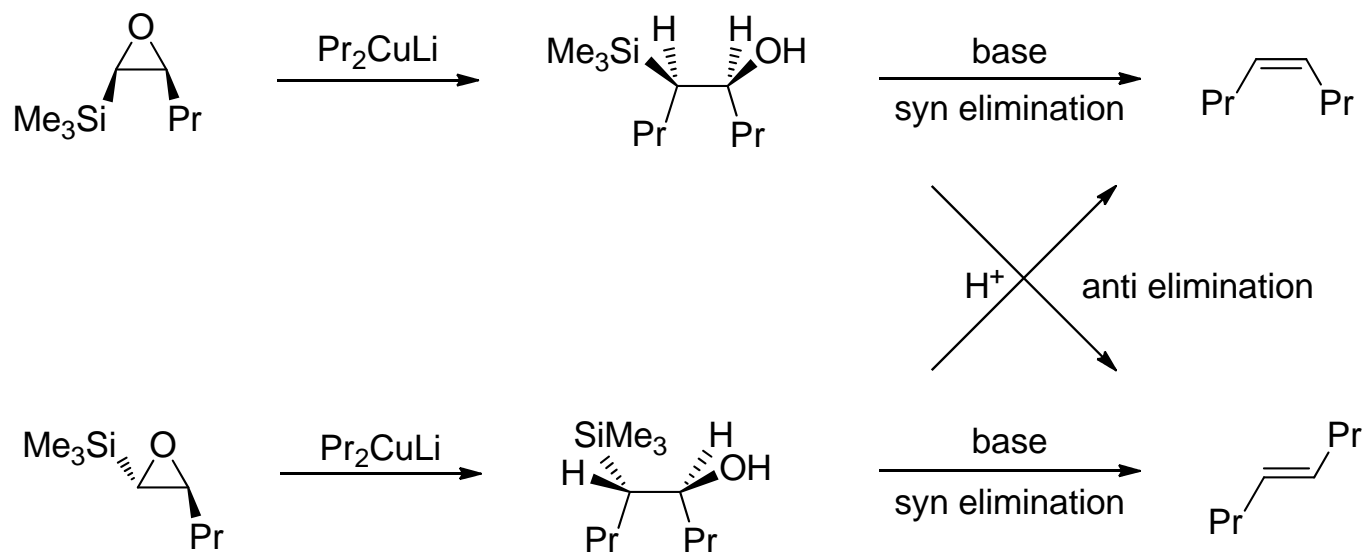
Silicium

Peterson olefination



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

Stereochemistry of the *Peterson*-elimination

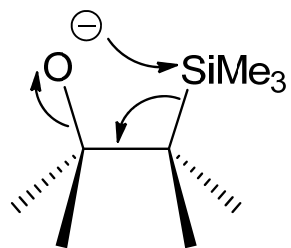


P. F. Hudrlik, D. Peterson, R. J. Rona *J. Org. Chem.* **1975**, *40*, 2263

Silicium

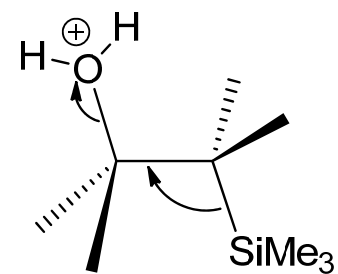
key steps:

basic
media



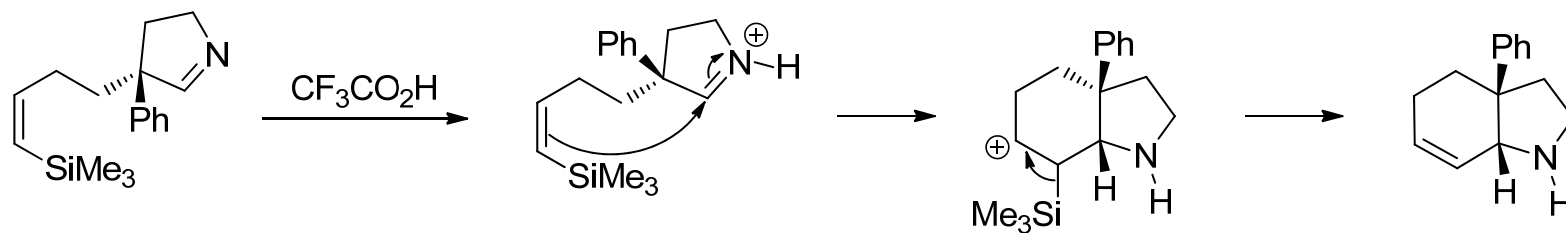
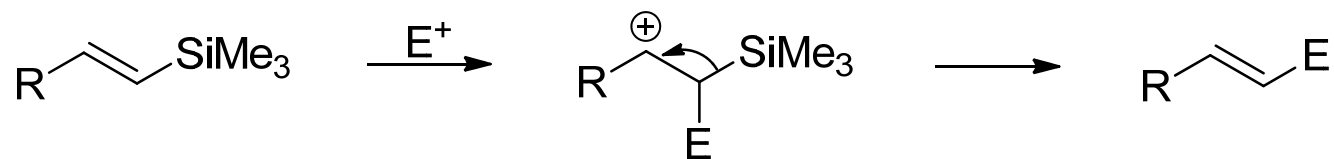
syn elimination

acidic
media



anti elimination

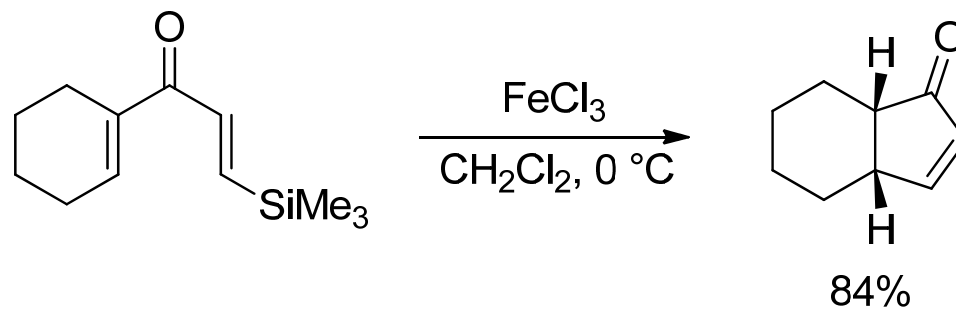
Reactivity of alkenylsilanes



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

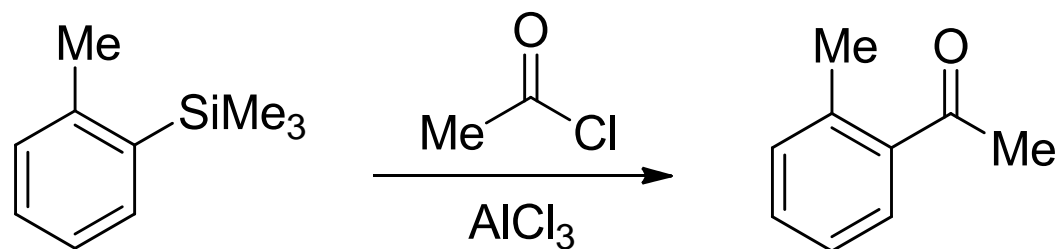
Reactivity of alkenylsilanes

Sila-Nazarov-reaction



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

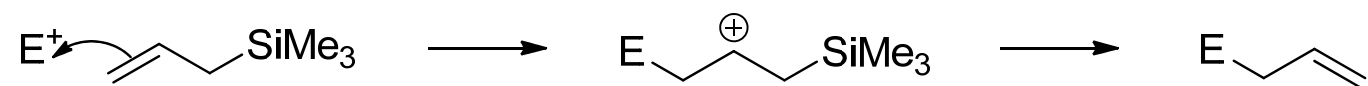
Aromatic ipso-substitution



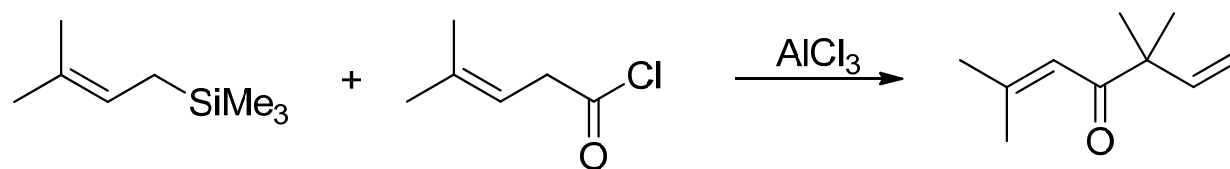
The reaction with ArSnMe_3 is 10^4 time faster

Allylic silanes in organic synthesis

General reactivity

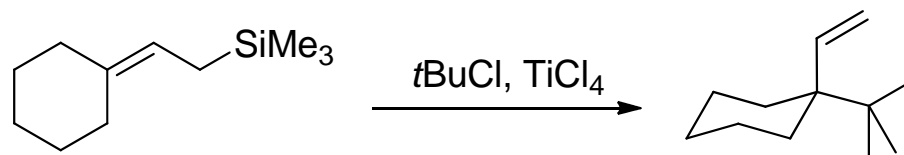


Acylation

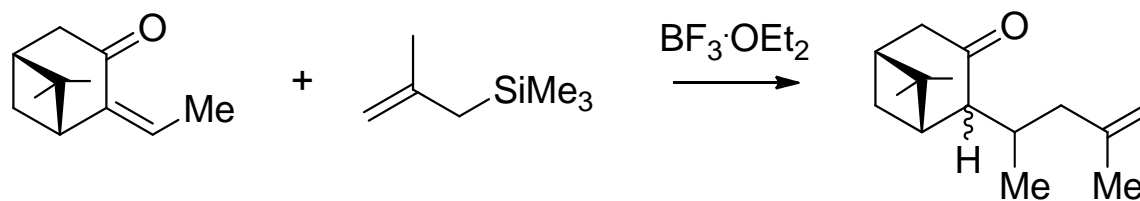


Allylic silanes in organic synthesis

Allylation



1,4-addition

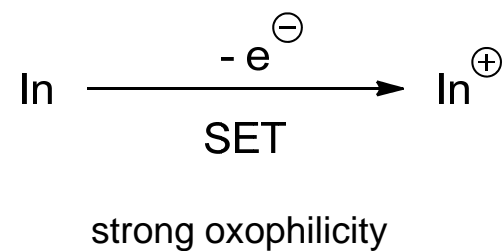


T. Yanami, M. Miyashita, A. Yoshikoshi, *J. Chem. Soc. Chem. Commun.* **1979**, 525.

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



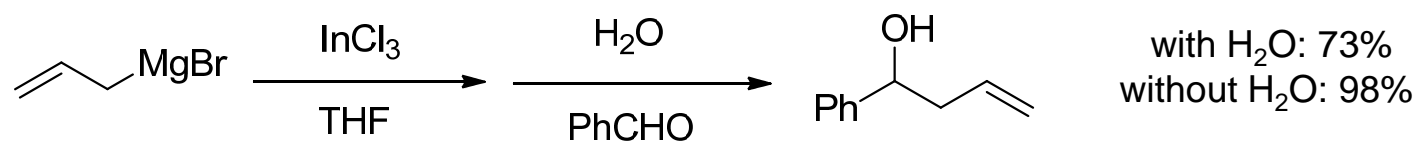
The first ionization potential of indium (5,8 eV)
is close to lithium and sodium

Key contributions:

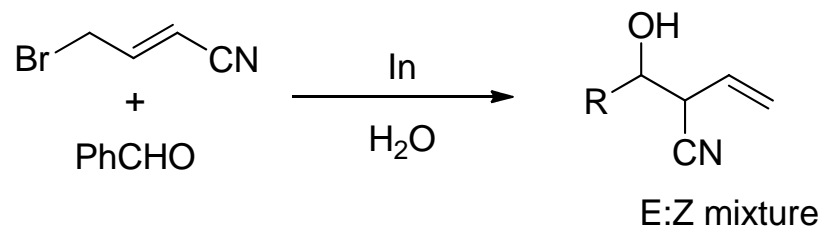
S. Araki *Main Group Metals in Organic Synthesis* **2004**, 1, 323

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

Indium. Allylation reactions

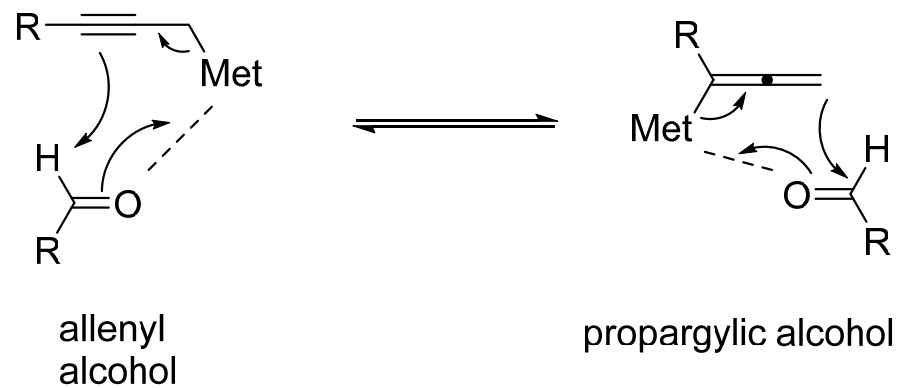
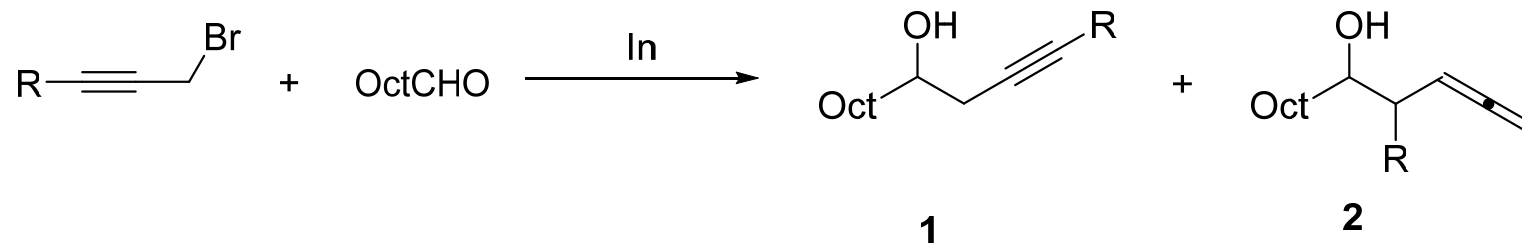


S. Akira, *J. Chem. Soc. Perkin Trans. I*, **1991**, 2395



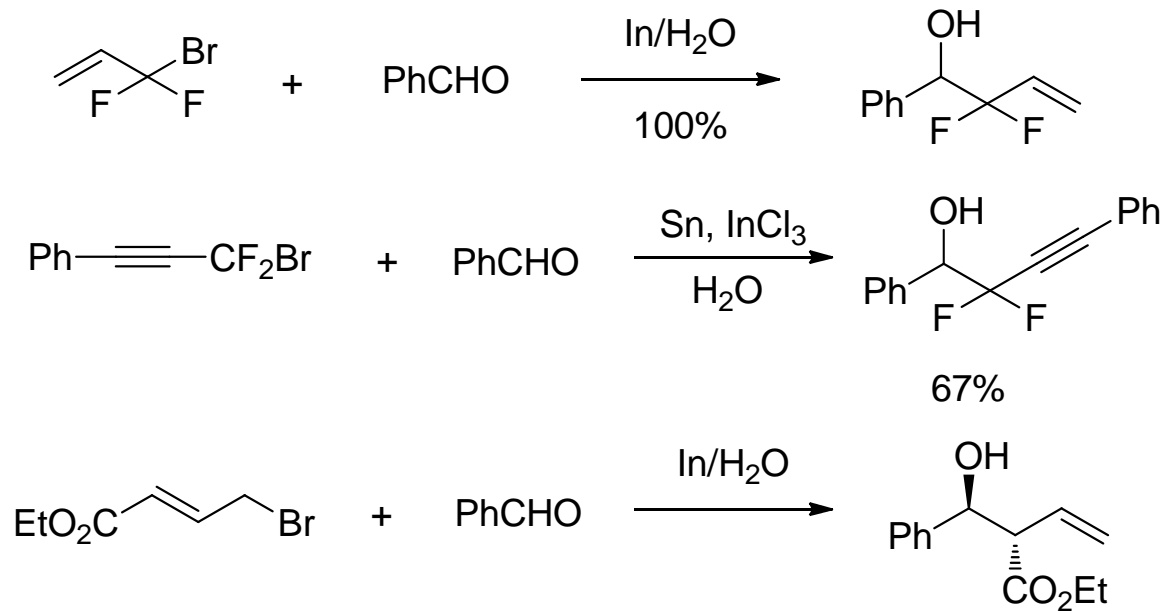
B. Manze, *Synth. Commun.* **1996**, 26, 3179

Indium



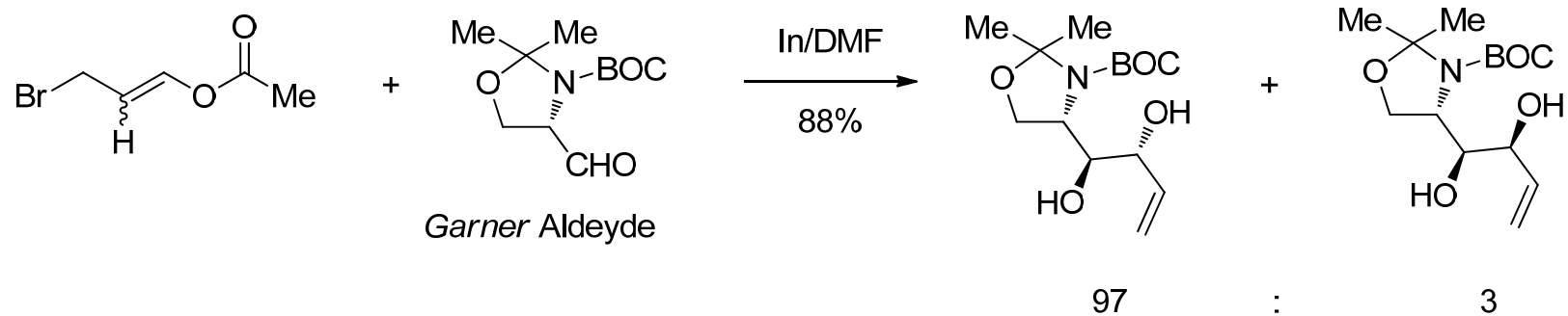
R	Conditions	Yield	Ratio
Me ₃ Si	THF, InF ₃ (10 mol%)	93	1 : 2 99:1
<i>i</i> Pr ₃ Si	THF:H ₂ O (1:5)	52	5:95

Indium

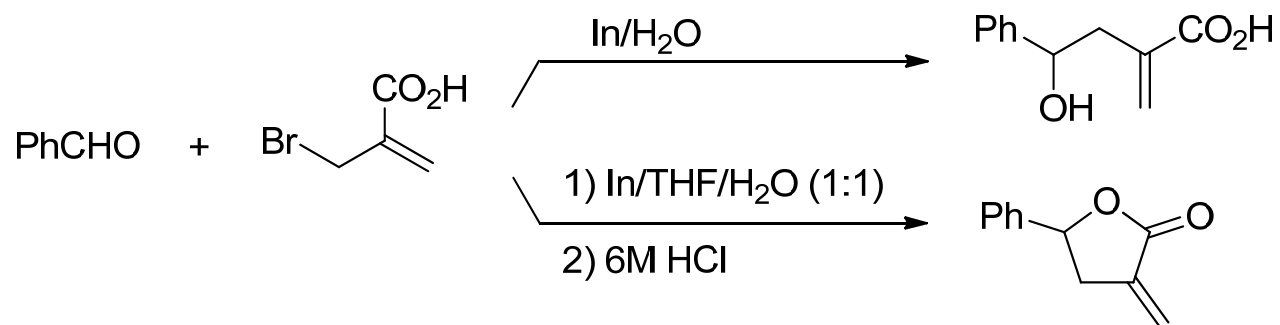


without $\text{La}(\text{OTf})_3$: 59% anti:syn = 86 : 14
with $\text{La}(\text{OTf})_3$: 99% anti:syn = 90 : 10

Indium

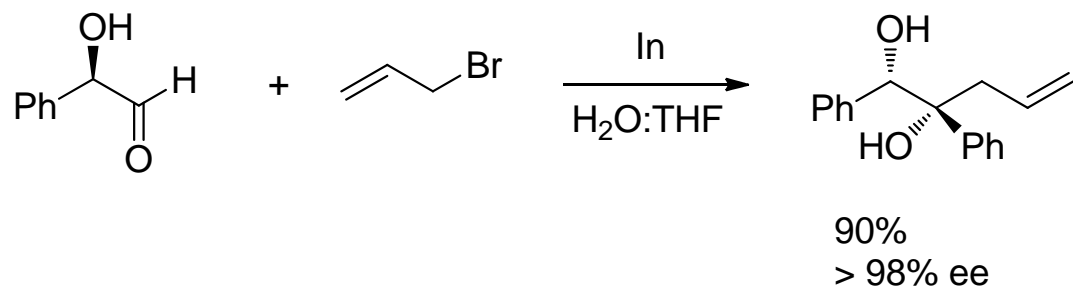
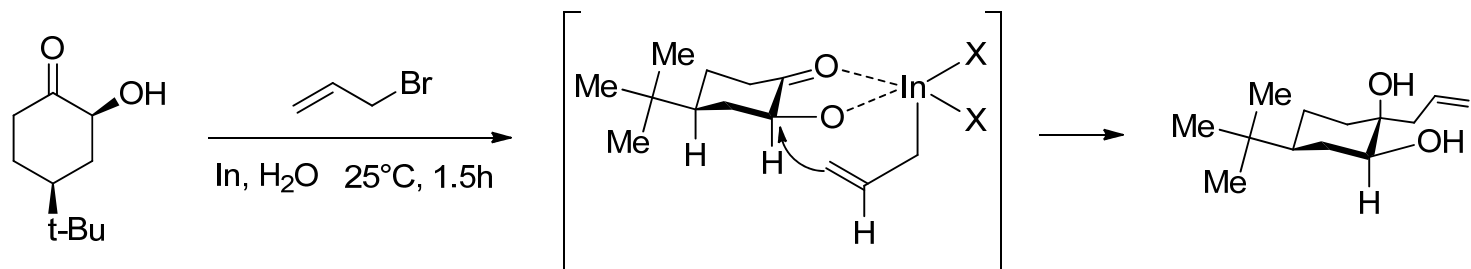


M. Lombardo, *Pure Appl. Chem.* **2004**, 76, 657



T. H. Chan, *J. Org. Chem.* **1995**, 60, 4228

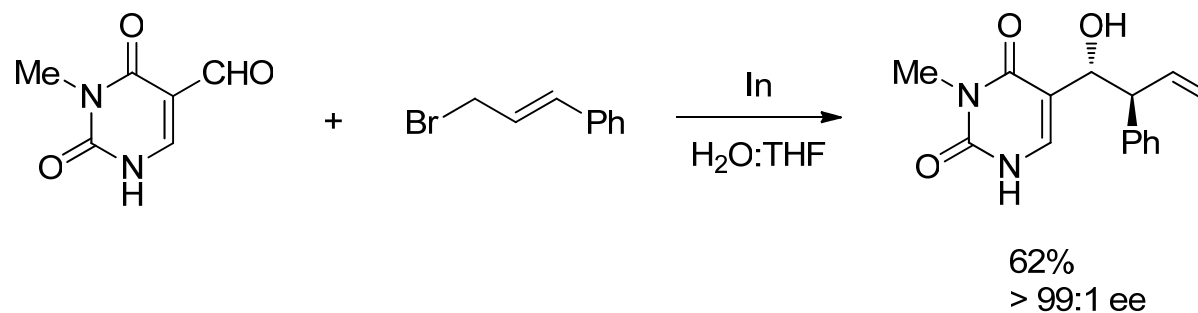
Indium



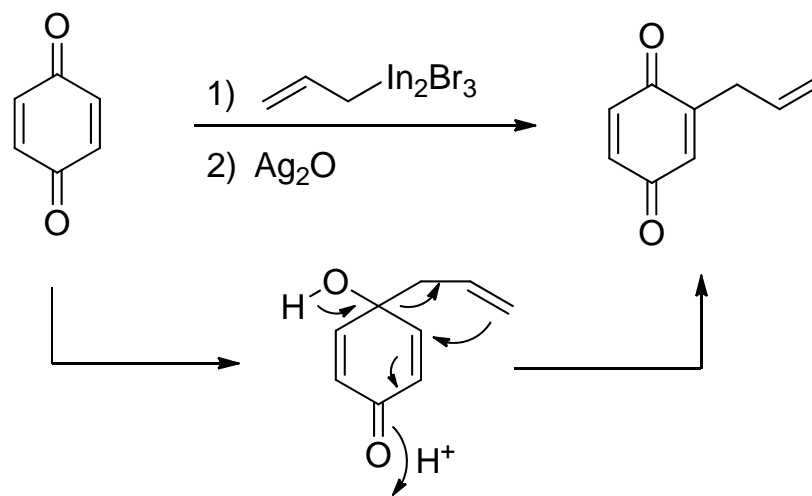
L. A. Paquette, *Org. Lett.* **2000**, 2, 1263

Indium

Applications in nucleoside chemistry:

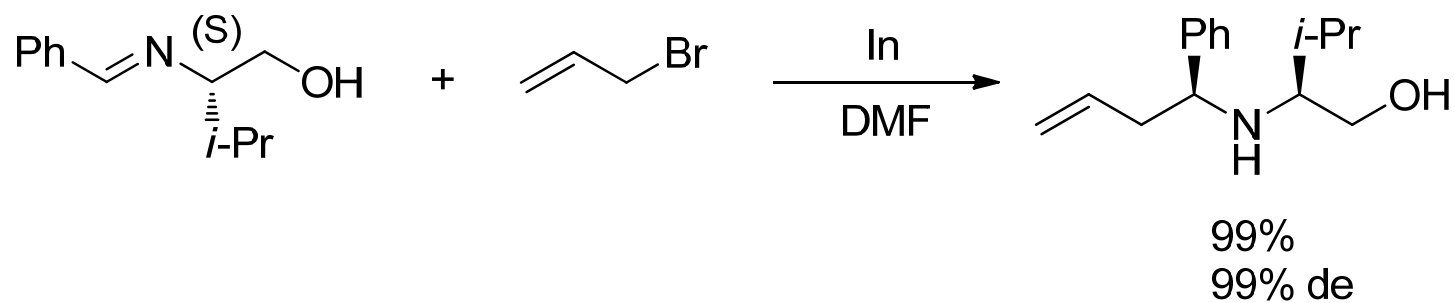


S. Kumar, *Tetrahedron Lett.* **2001**, 42, 7039

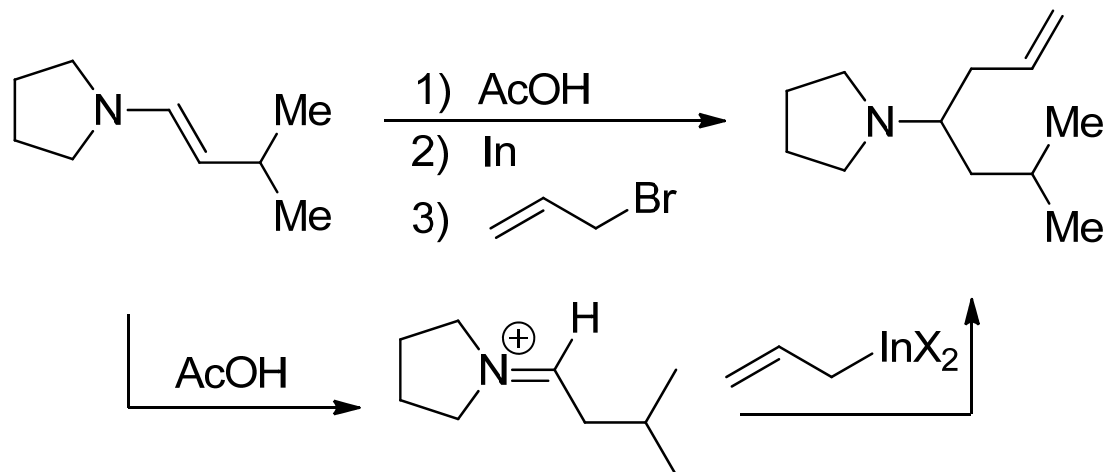


S. Akiva, *J. Organomet. Chem.* **1991**, 415, 7

Indium



T. P. Loh, *Tetrahedron Lett.* **1997**, 38, 865

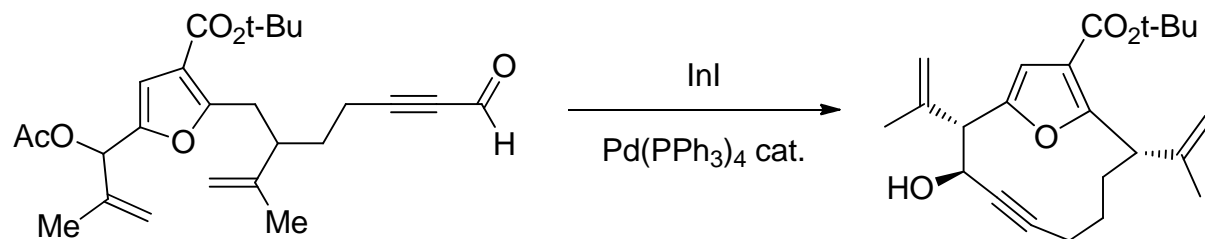


P. Mosset *Tetrahedron Lett.* **1995**, 36, 6055

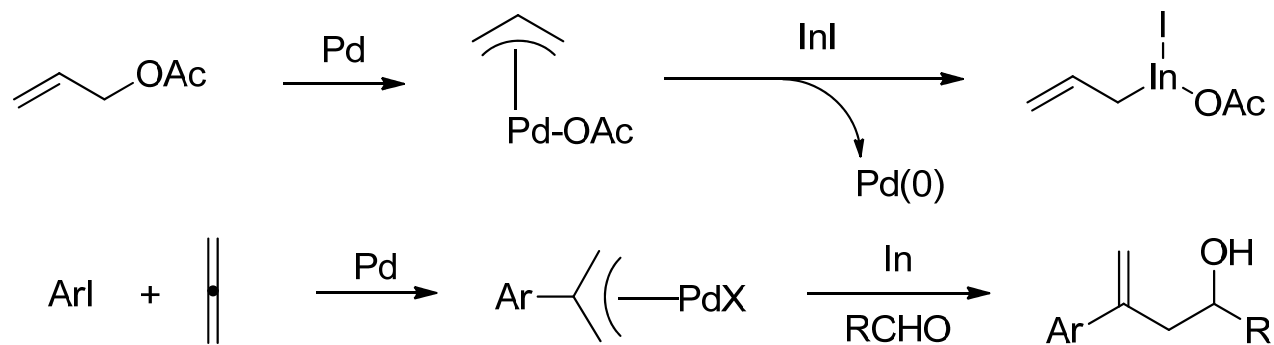
P. Mosset *Chem. Eur. J.* **1997**, 3, 1064

Indium

Applications in natural product syntheses:

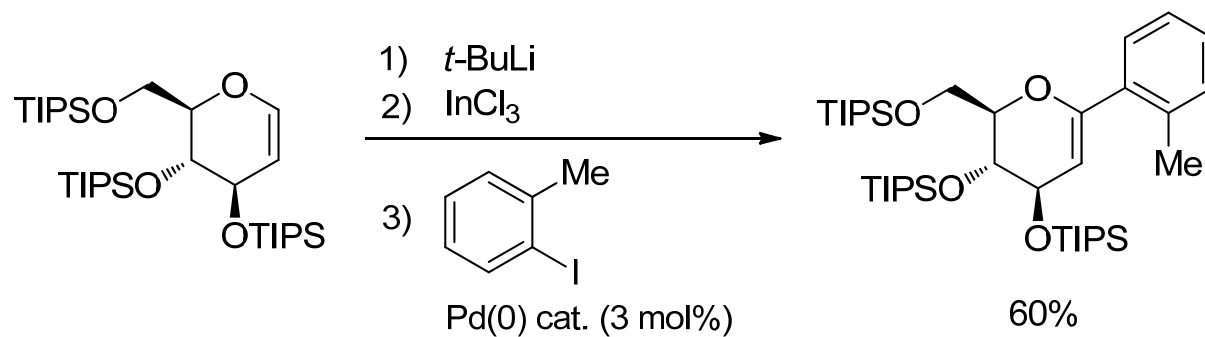


J. A. Marshall, *J. Org. Chem.* **1999**, *64*, 5193



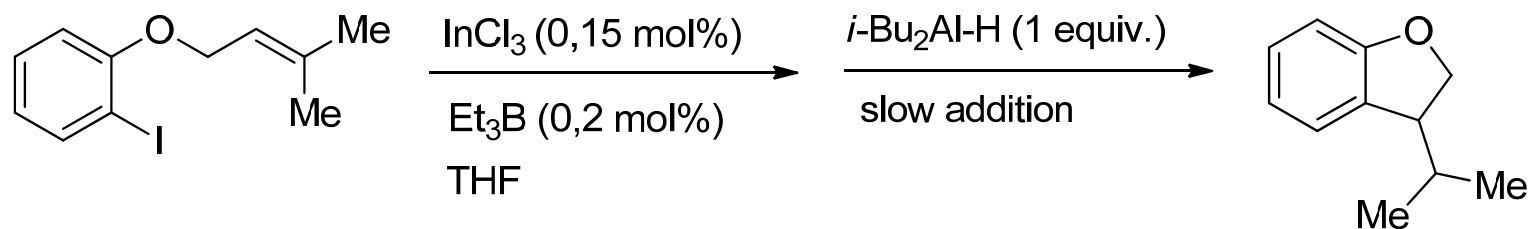
S-K. Kang S-W. Lee J. Jung Y. Lim *J. Org. Chem.* **2002**, *67*, 4376

Indium



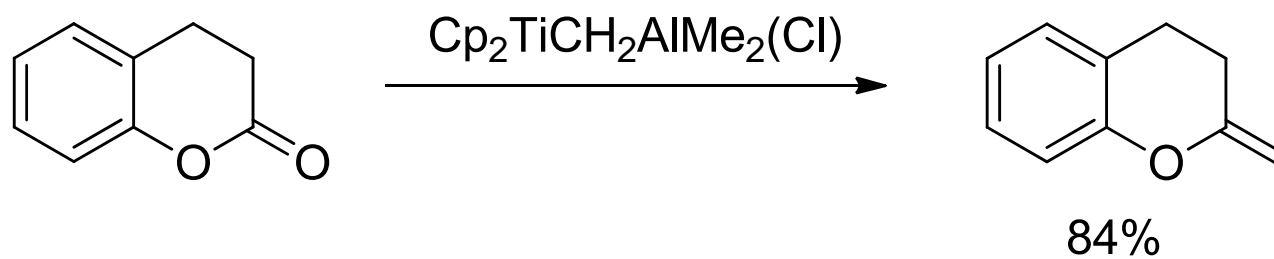
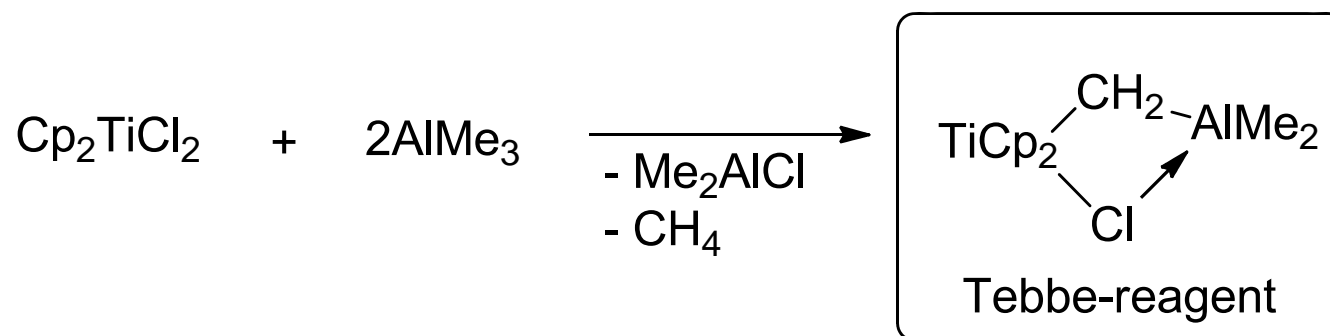
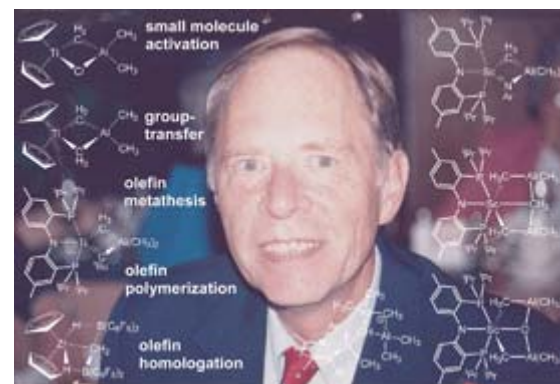
U. Lehmann, *Org. Lett.* **2003**, 5, 2405

radical reaction



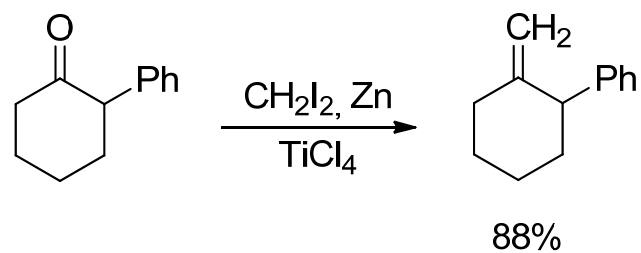
K. Oshima, *Tetrahedron*, **2003**, 59, 6627

Early transition metal organometallics: Titanium

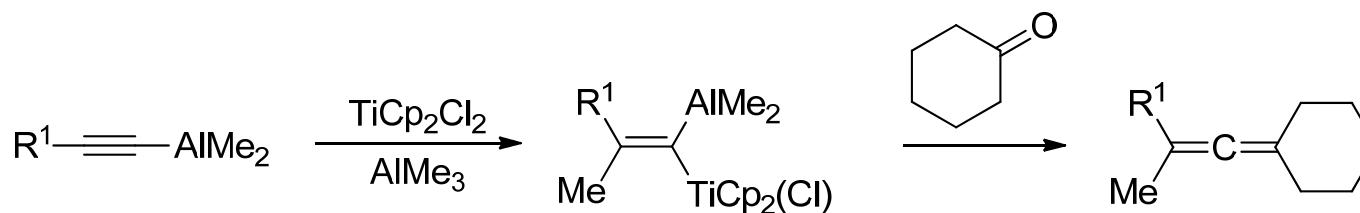
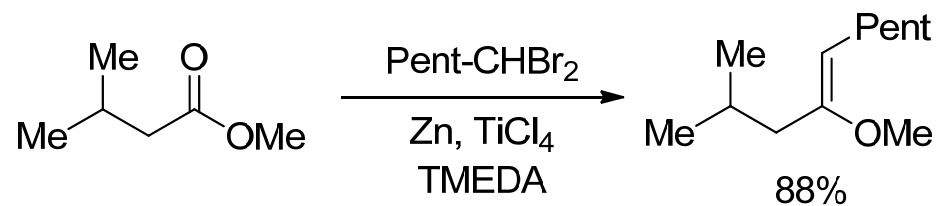


Titanium

Lombardo-reagent

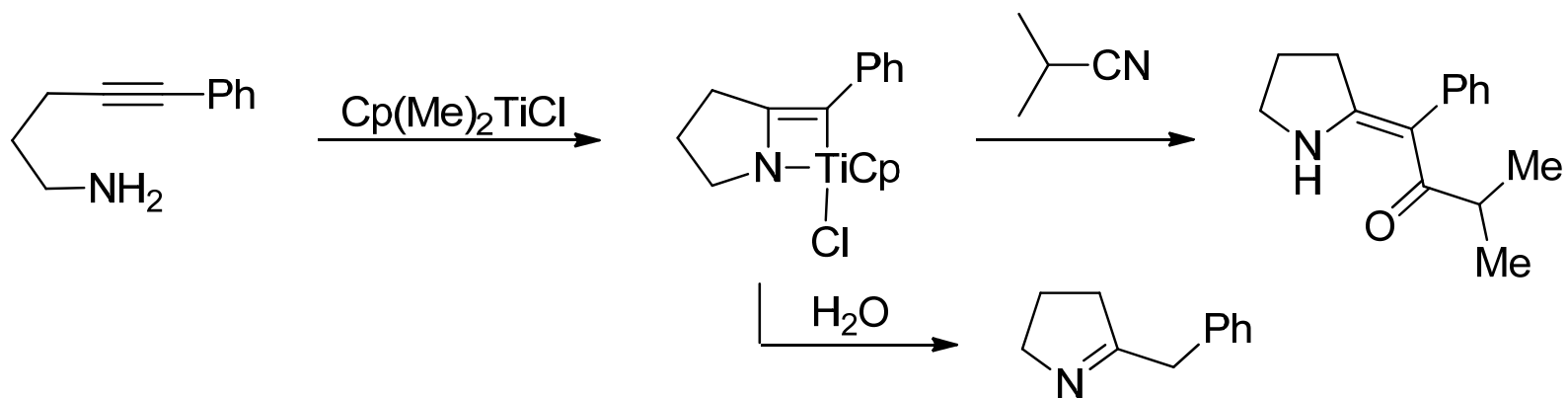


K. Takai, *J. Org. Chem.* **1994**, 59, 2668



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

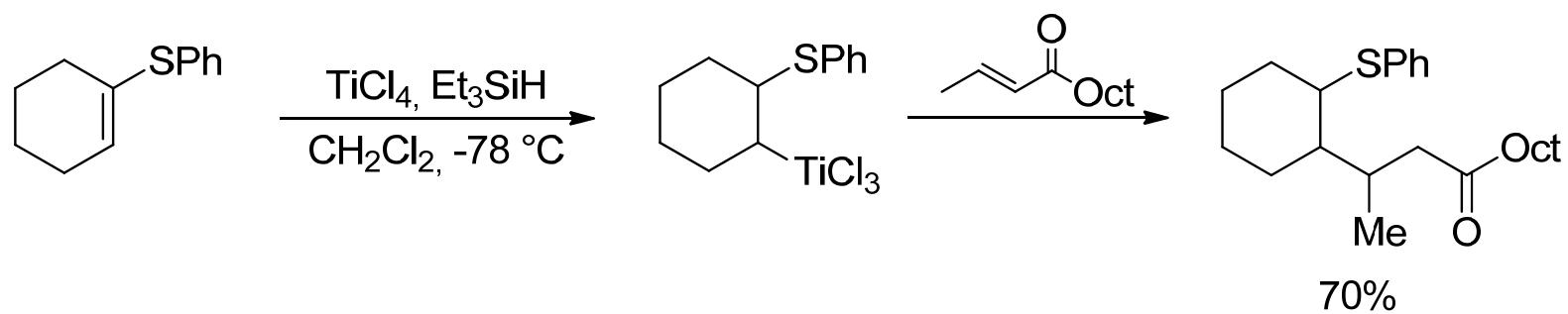
Titanium



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

Titanium

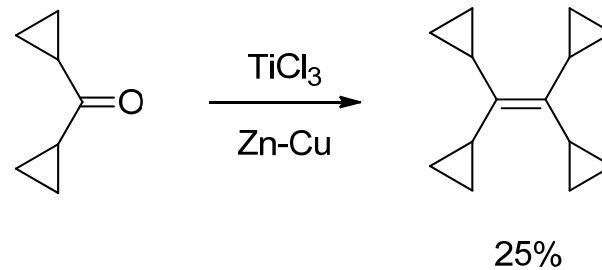
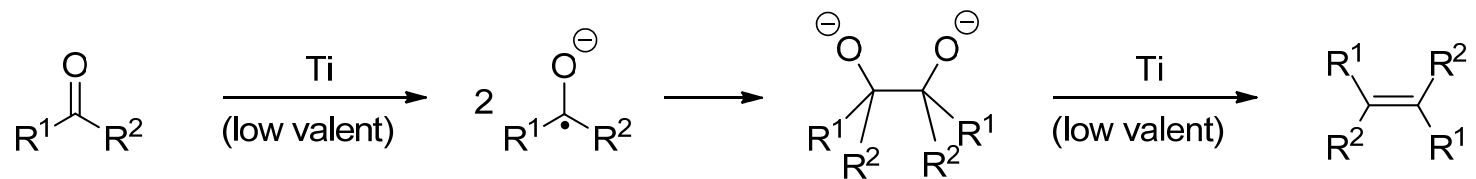
Hydrotitanation



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

Titanium

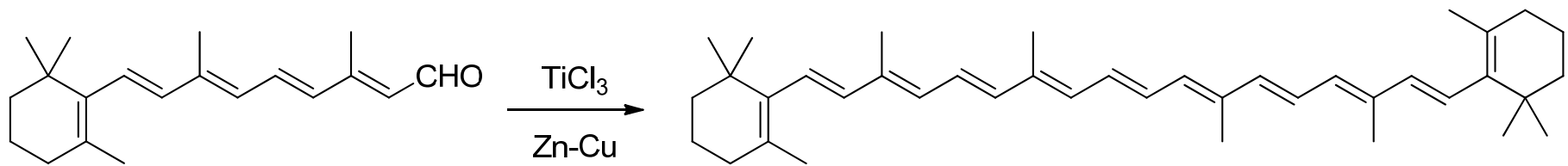
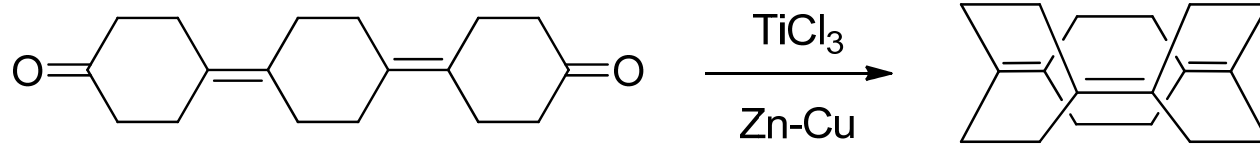
Reductive coupling: The McMurry Reaction



Review:

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

Titanium

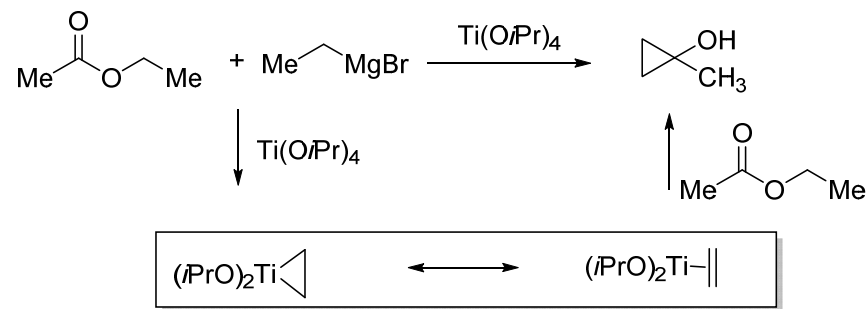


β -Caroten: 94%

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

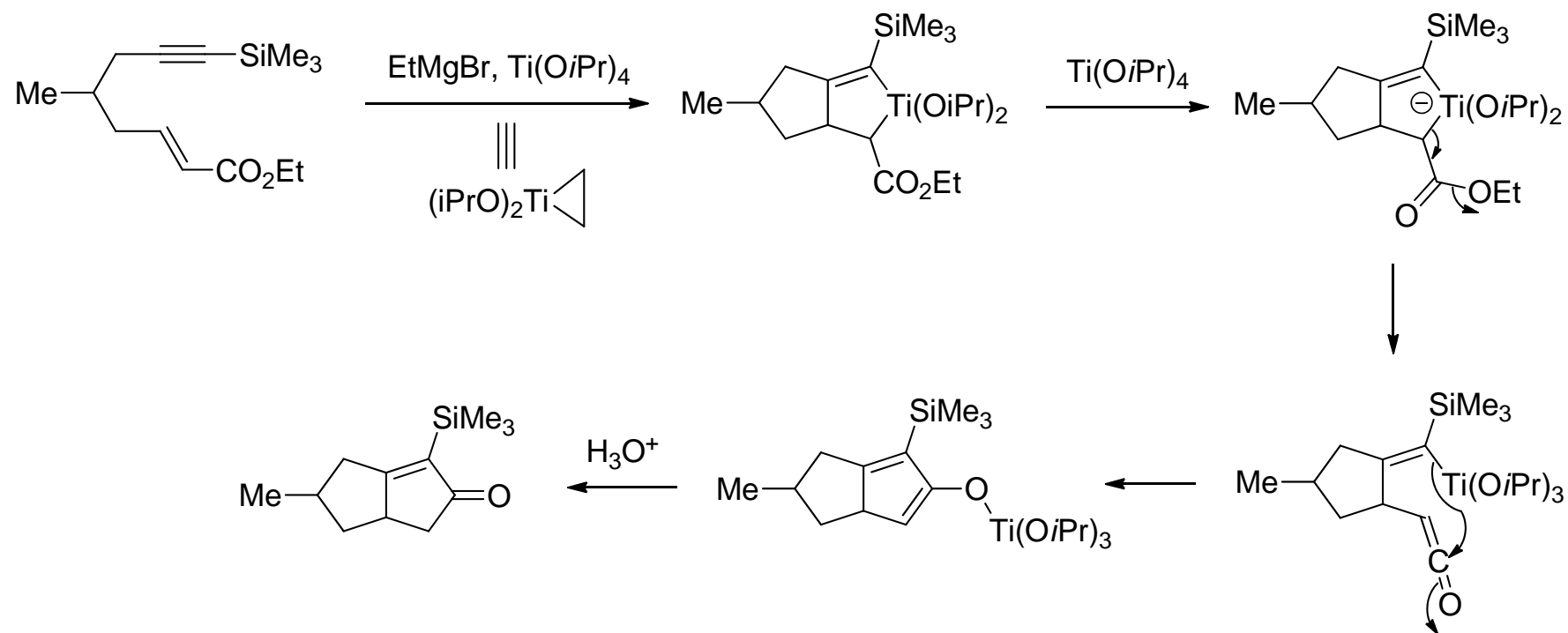
Titanium

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.

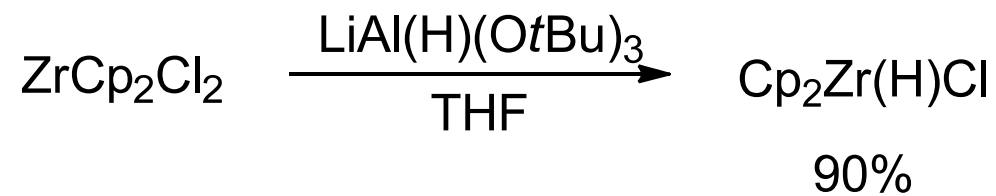
Titanium



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

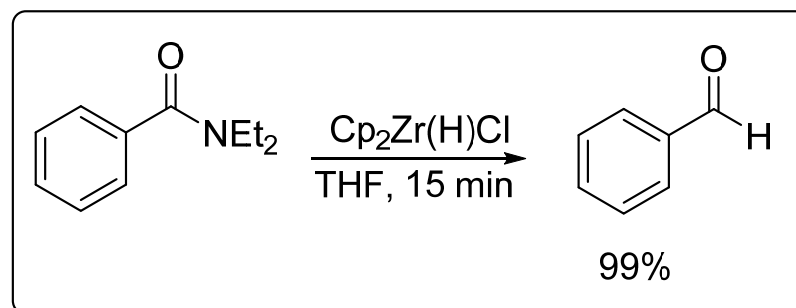
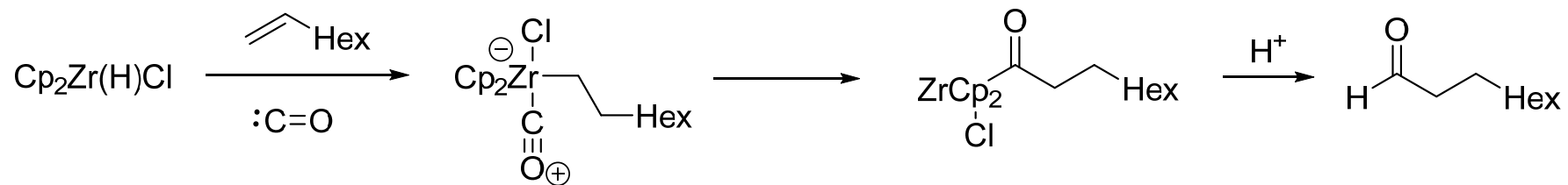
Early transition metal organometallics: Zirconium

Schwartz's reagent:



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

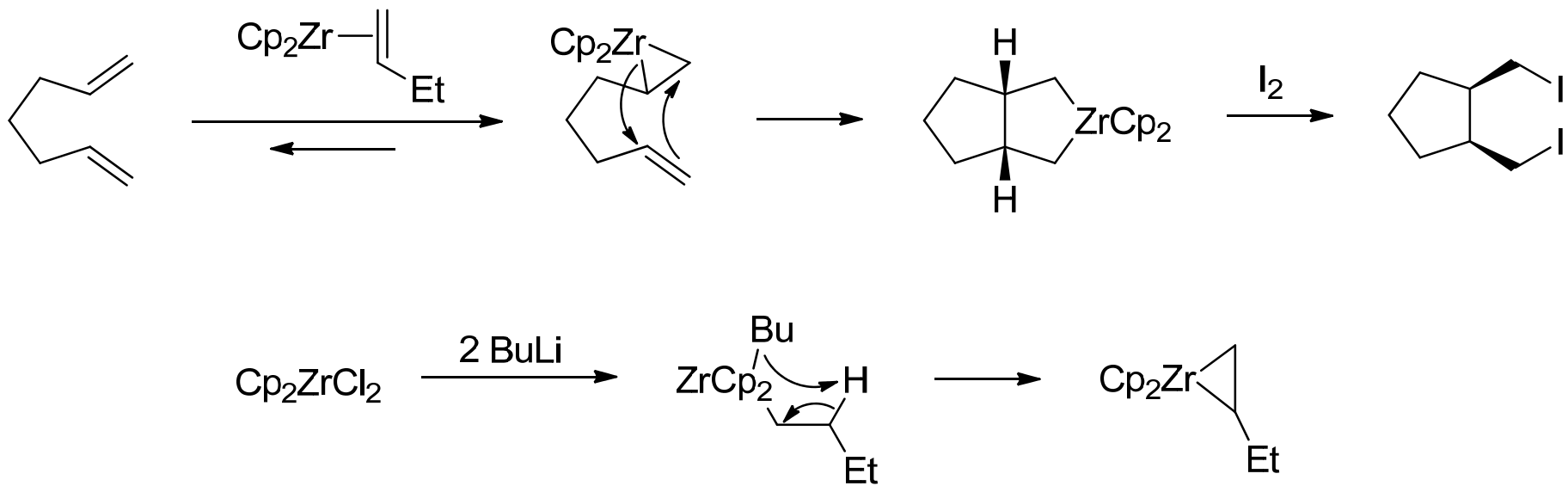
Zirconium



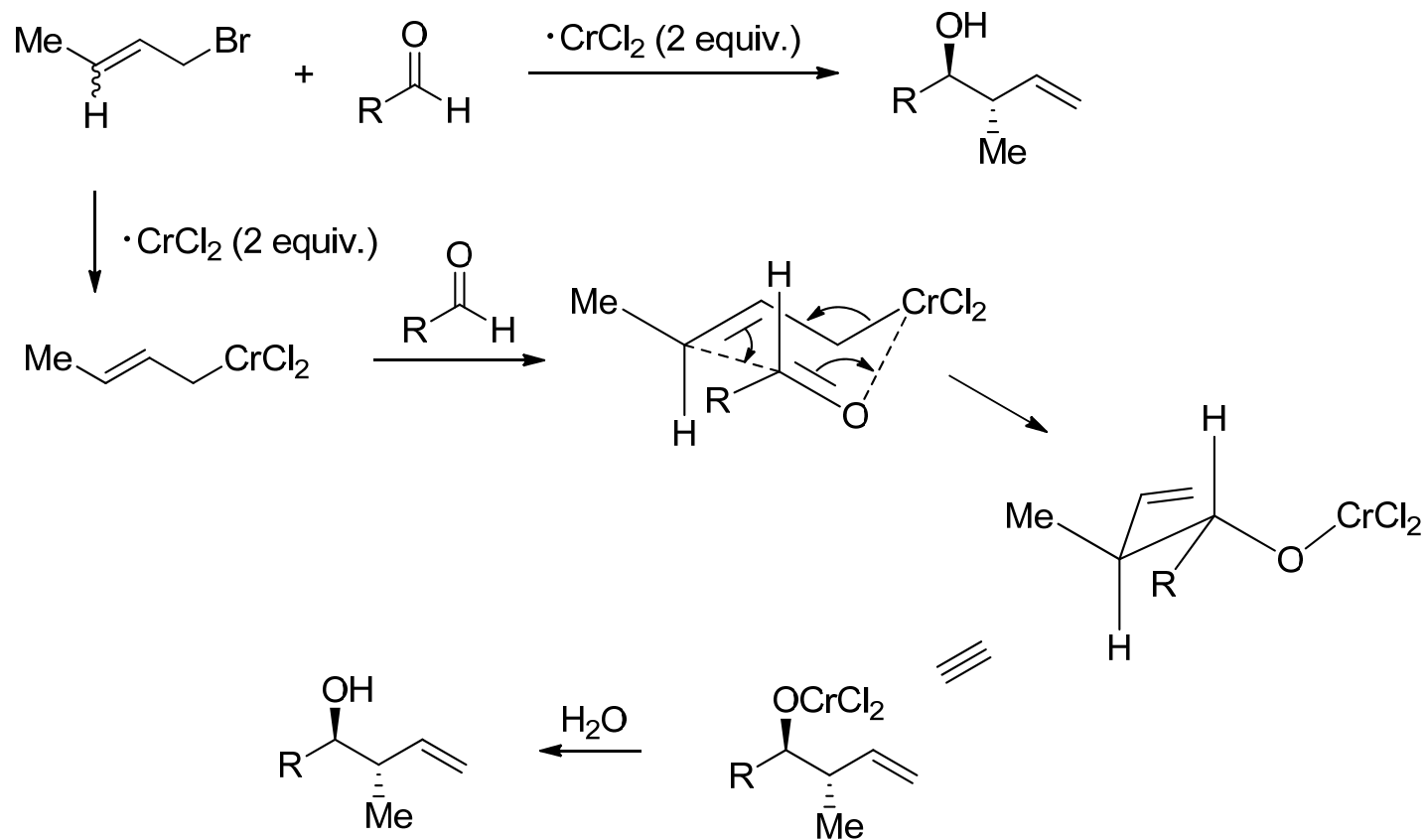
G. I. Georg *J. Am. Chem. Soc.* **2007**, 129, 3408

Zirconium

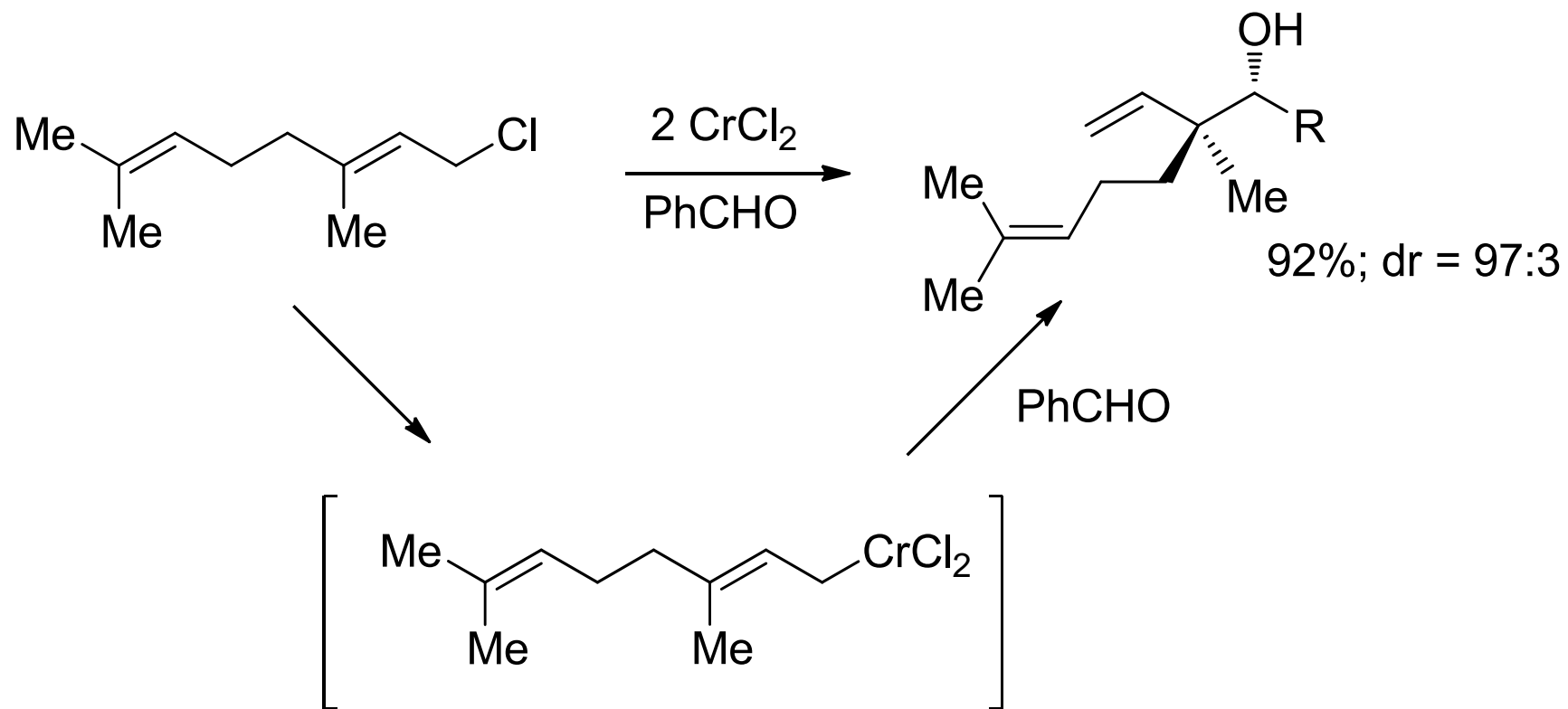
A Negishi reaction is involved:



Early transition metal organometallics: Chromium



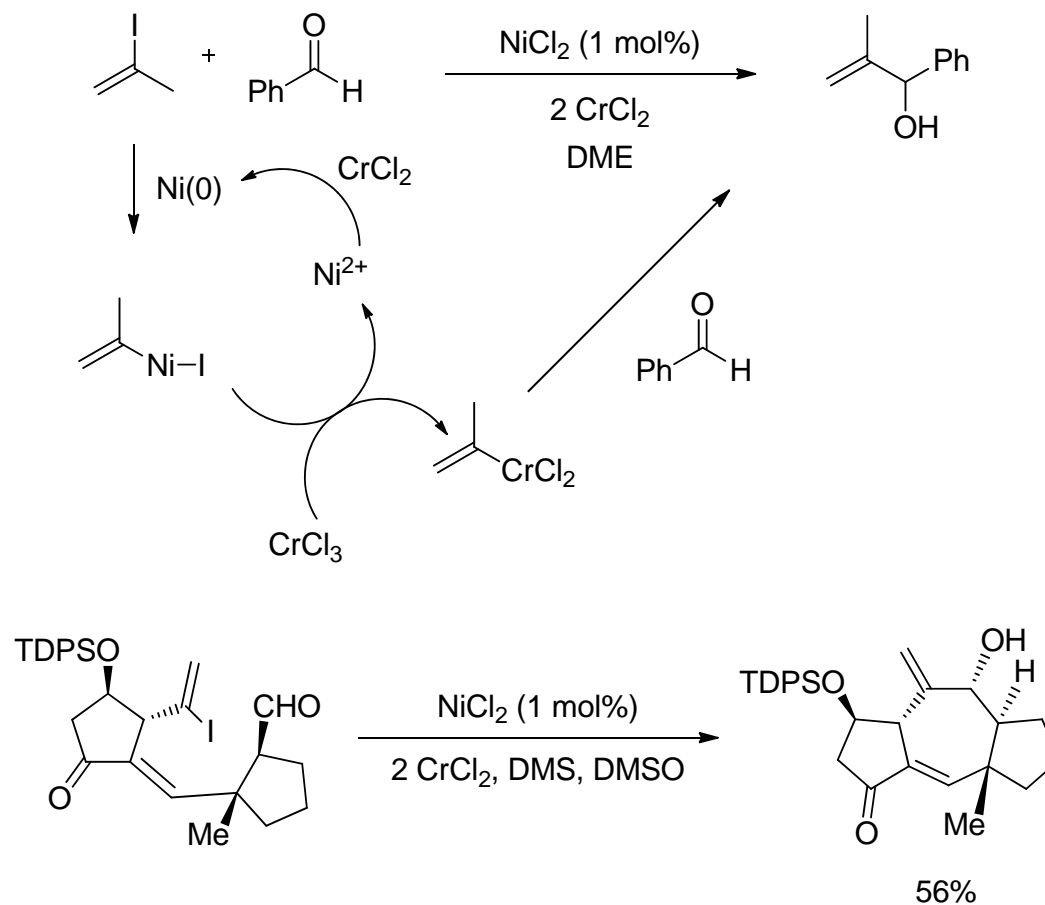
Chromium



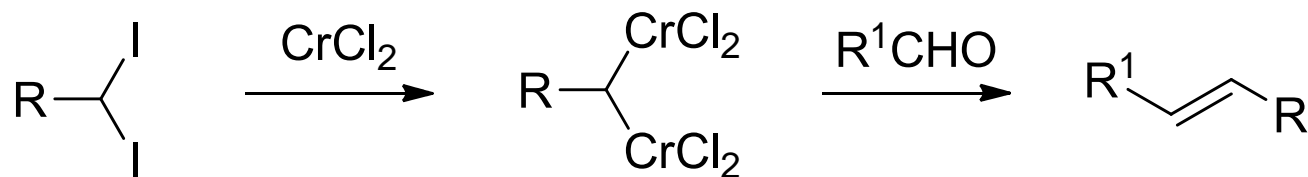
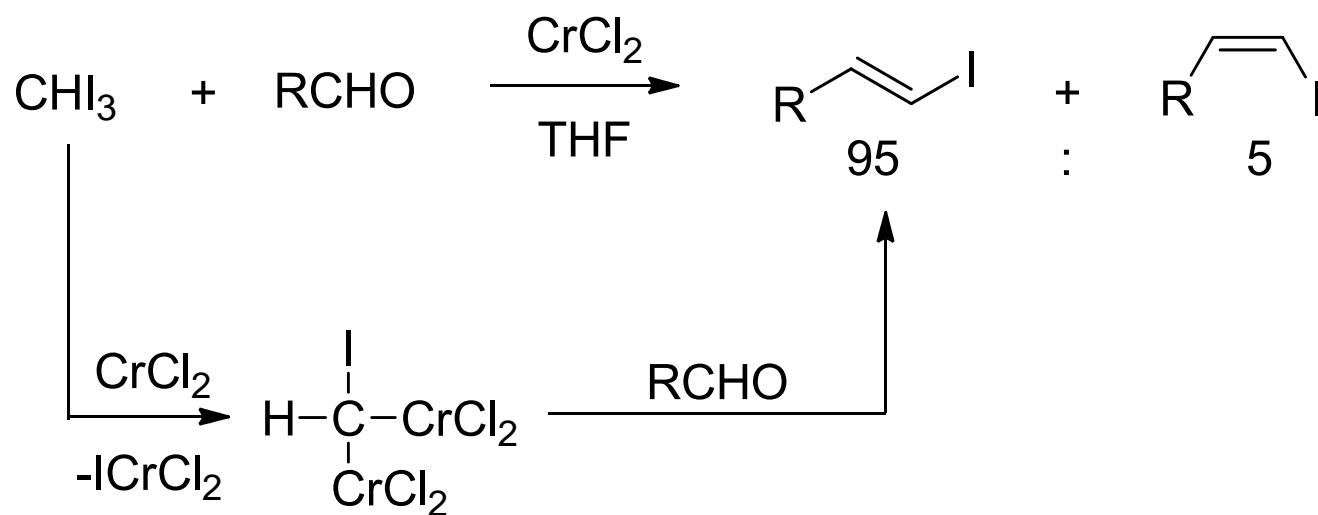
K. Belyk, M. J. Rozema, P. Knochel *J. Org. Chem.* **1992**, *57*, 4070.

Chromium

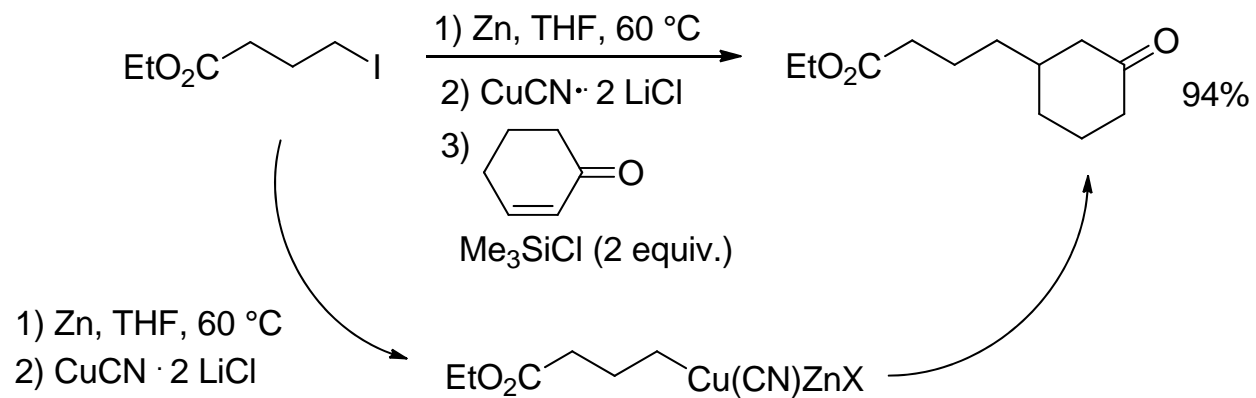
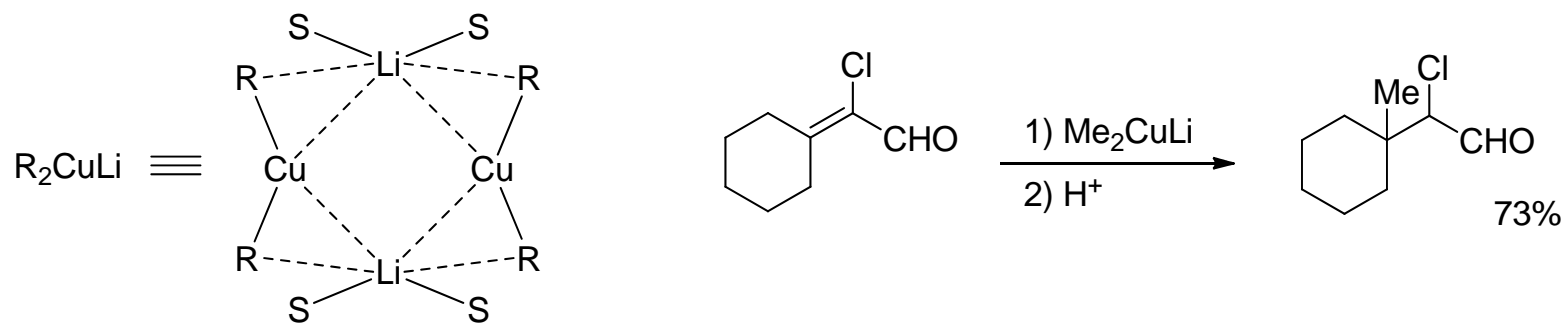
Hiyama-Kishi-reaction



Chromium

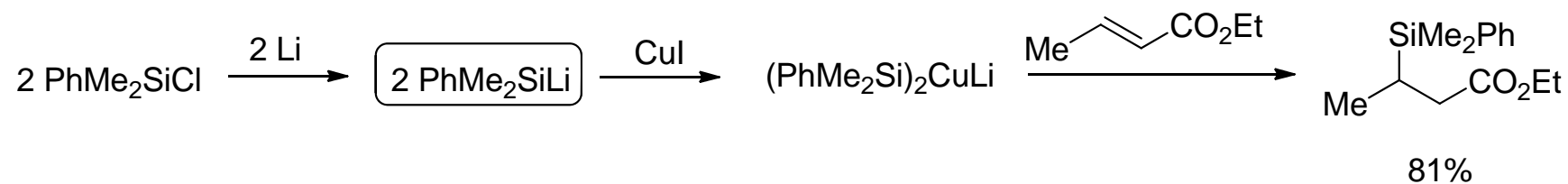


Early transition metal organometallics: Copper

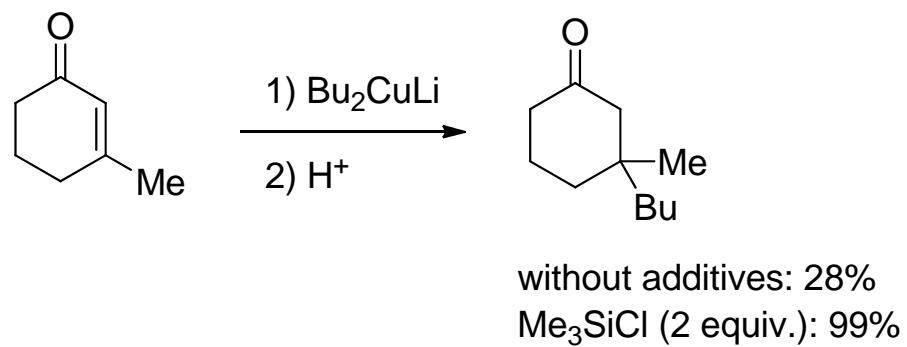


P. Knochel, et al. *J. Org. Chem.* **1988**, 53, 2390.

Copper

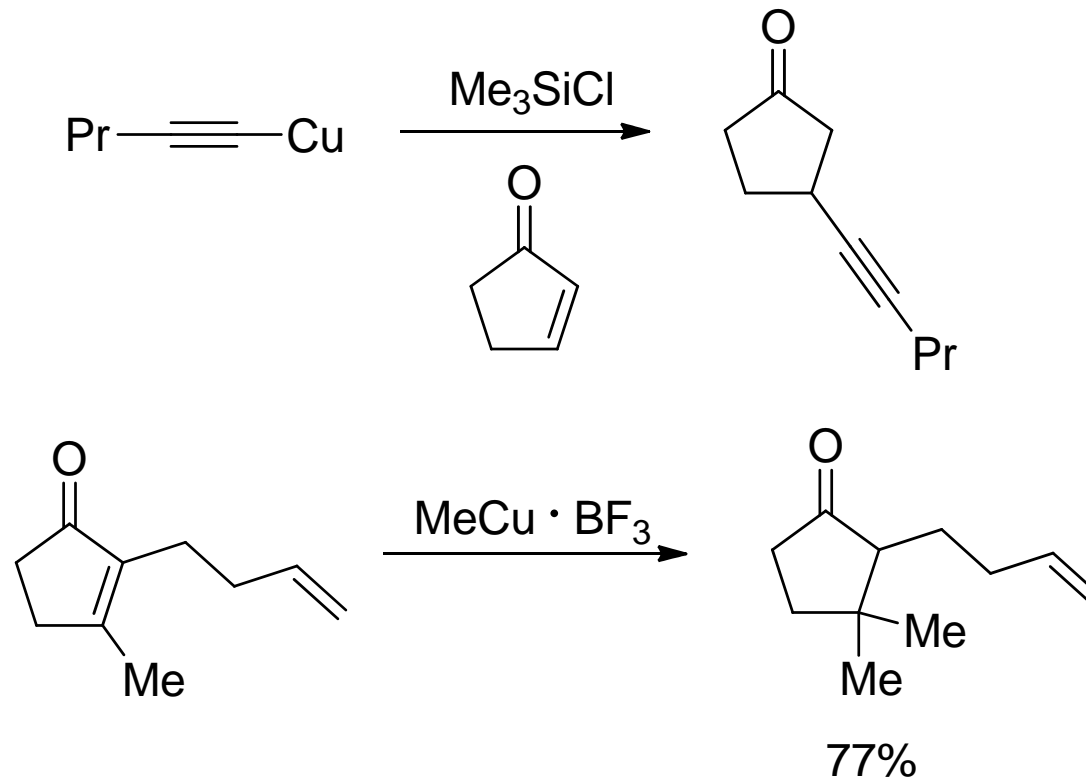


I. Fleming et al. *J. Chem. Soc., Perkin Trans.* **1998**, 1, 1209.



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

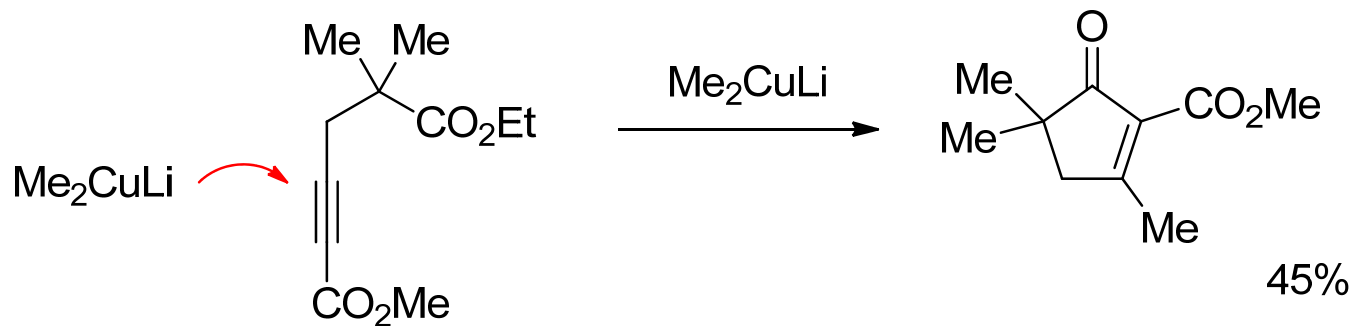
Copper-mediated 1,4-addition



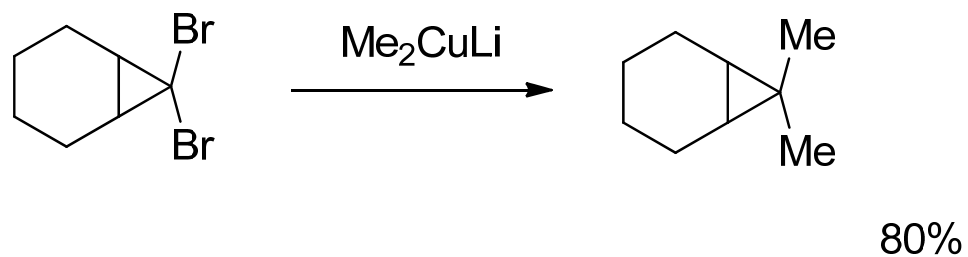
Y. Yamamoto, *Angew. Chem.* **1986**, 98, 945.

Copper-mediated reactions

Michael-addition



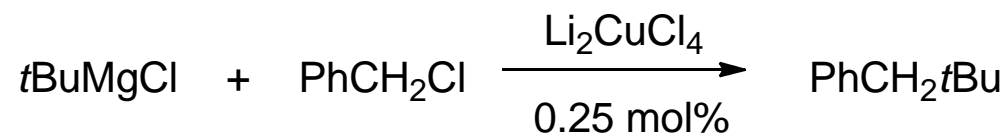
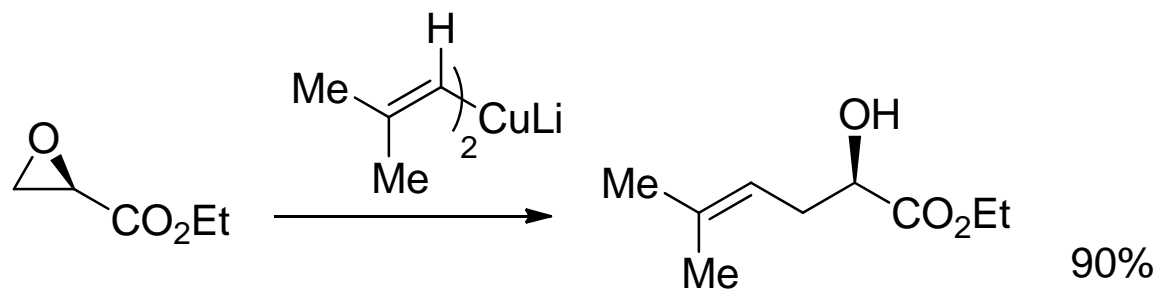
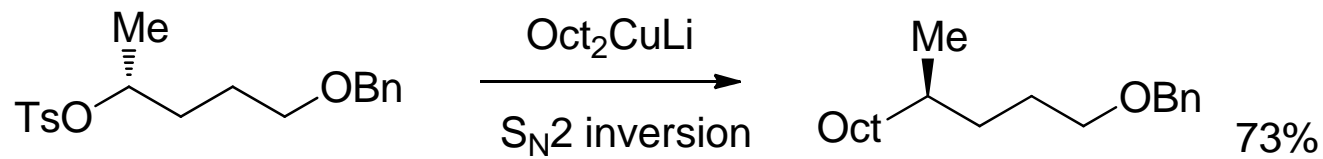
Substitution reactions



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

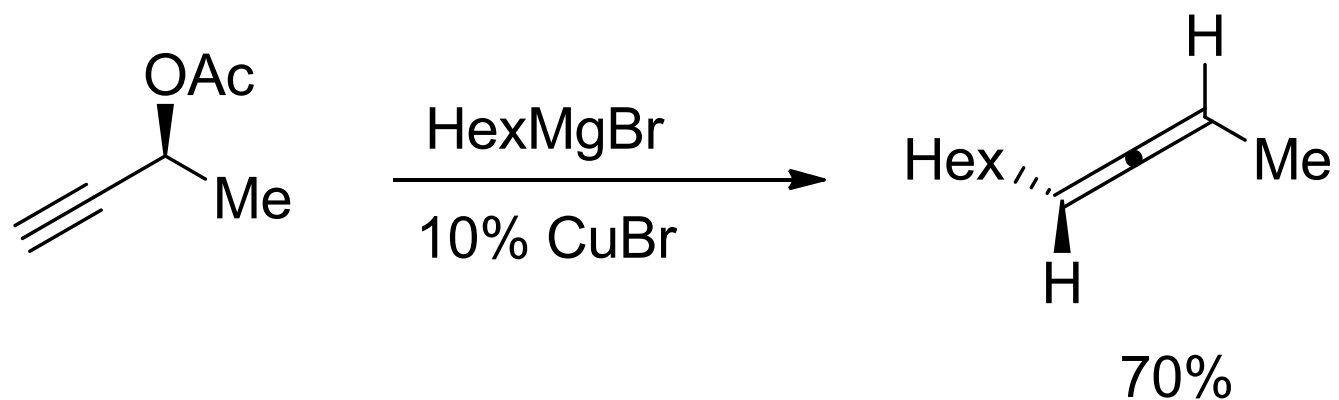
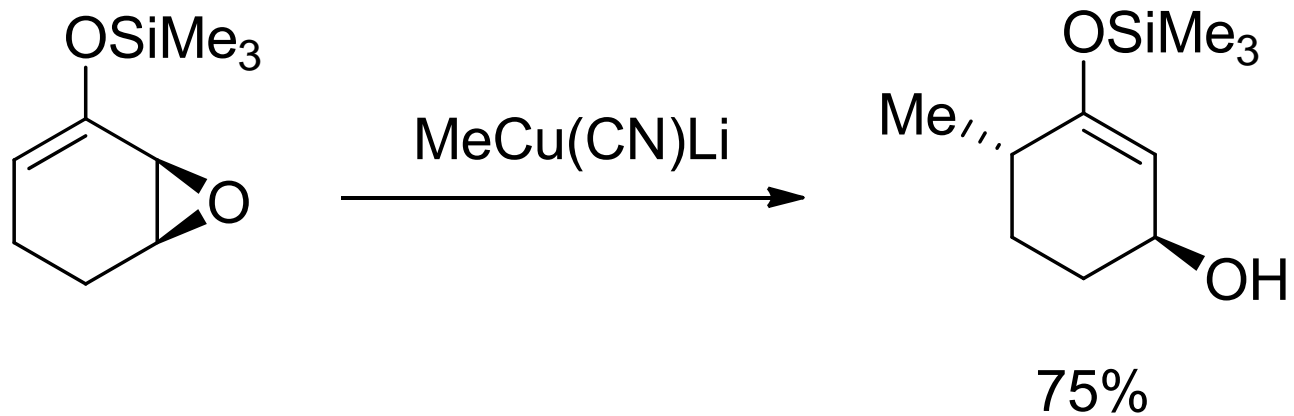
R. J. K. Taylor (Ed.), *Organocopper reagents*, Oxford University Press, Oxford, **1994**.

Copper; substitution reactions



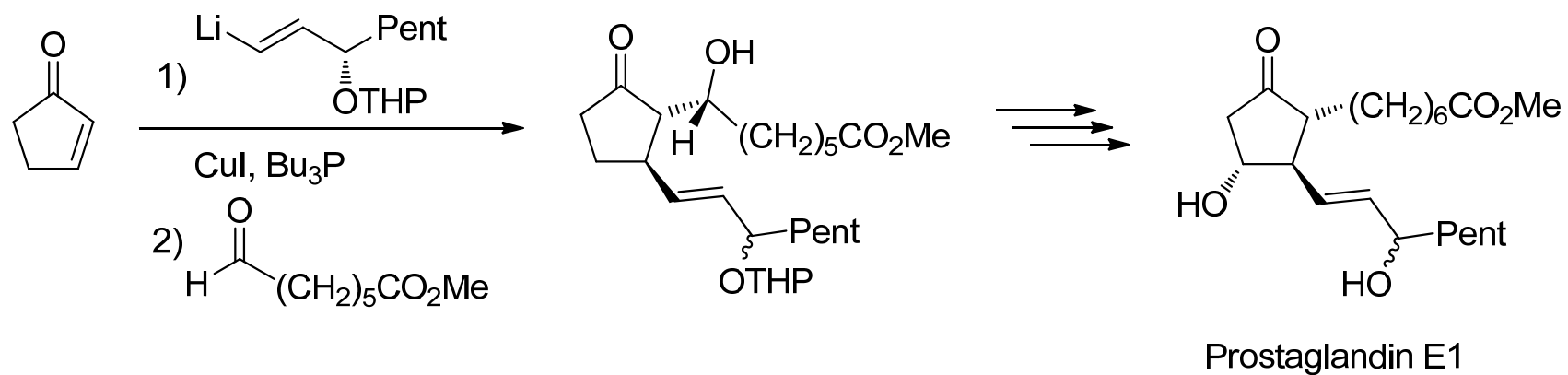
M. Larcheveque, Y. Petit, *Bull. Soc. Chim. Fr.* **1989**, 1, 130.

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

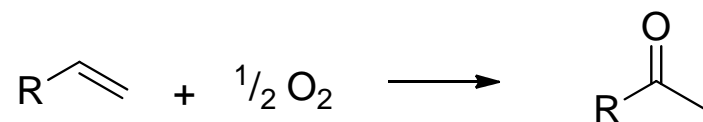
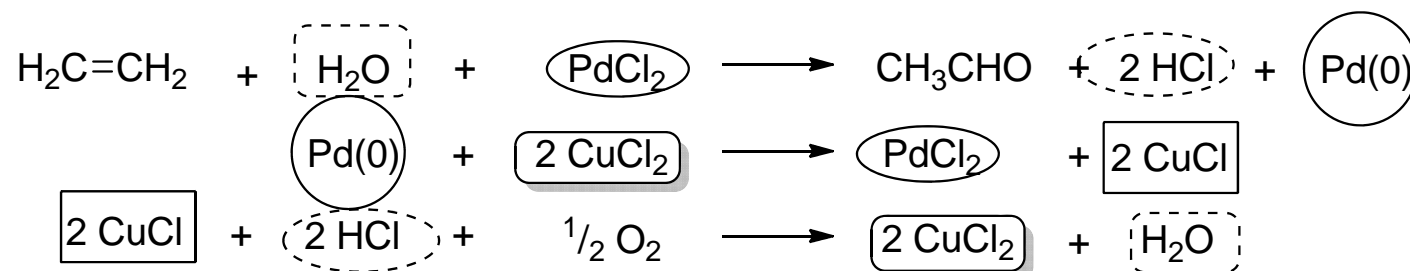
Pt: 3.3

Au: 1.9

Ru: 0.2

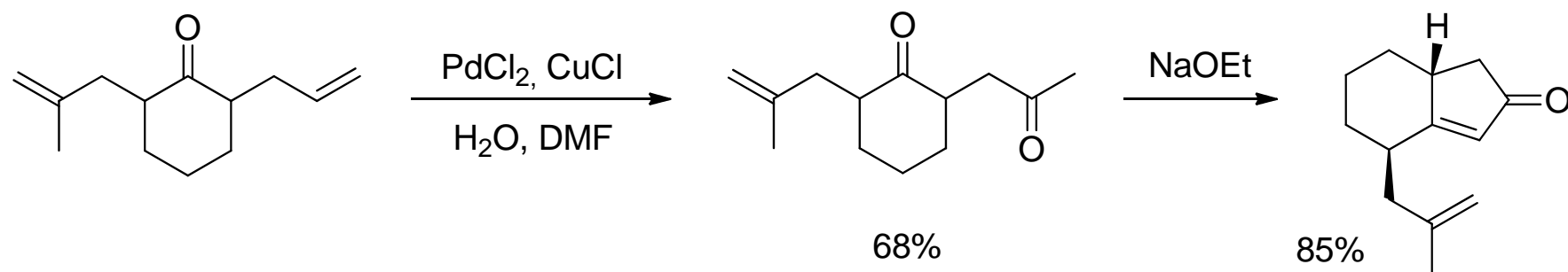
Rh: 2.8

Wacker-Reaction:



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

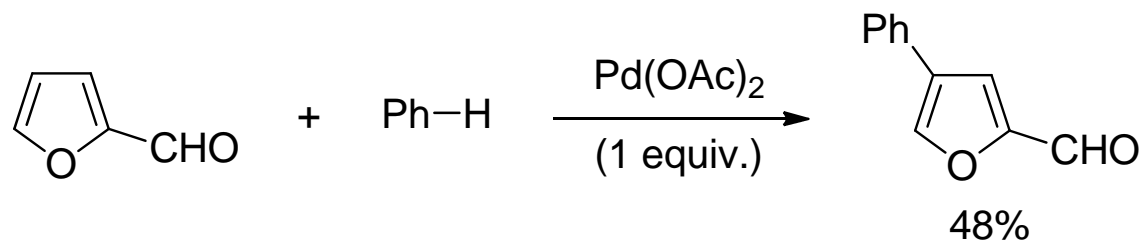
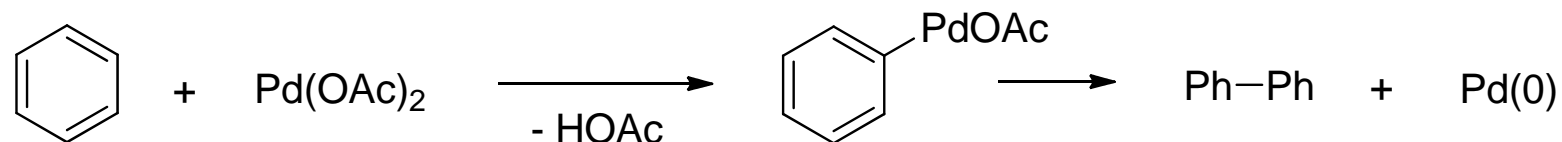
Palladium



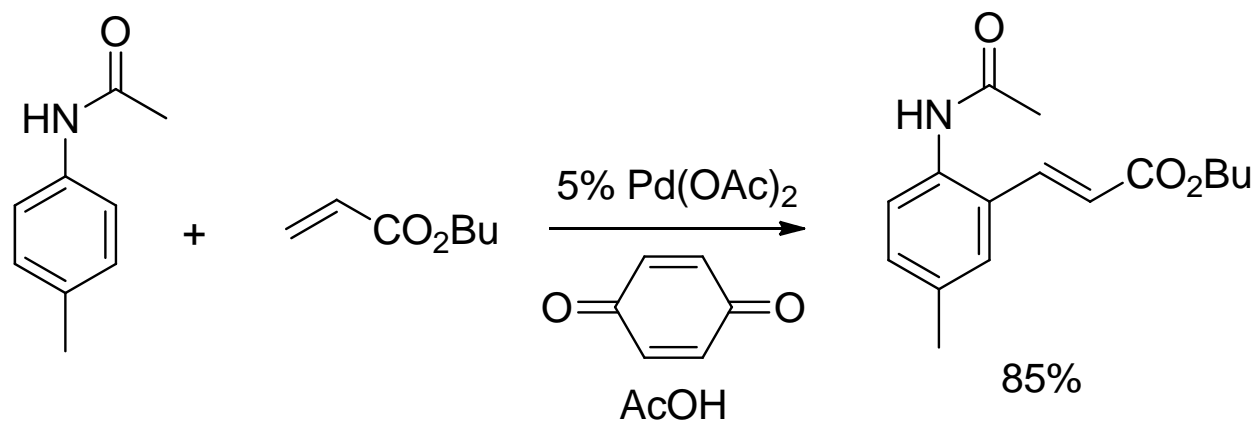
J. Tsuji, I. Shimizu, K. Yamamoto, *Tetrahedron Lett.* **1976**, 34, 2975.

Palladium

C-H activation



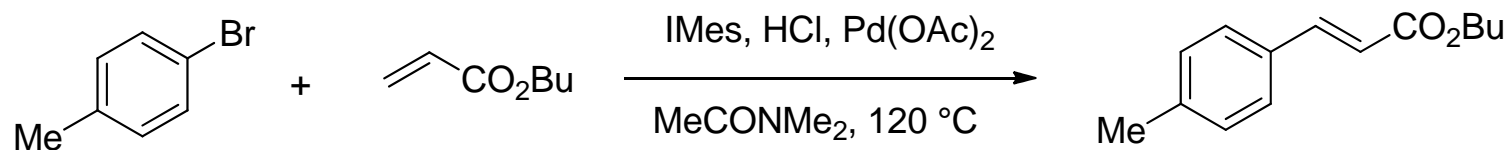
T. Itahara, *J. Org. Chem.* **1985**, *50*, 5272.



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

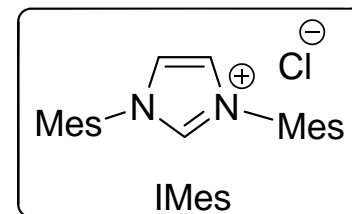
Palladium

Heck Reaction



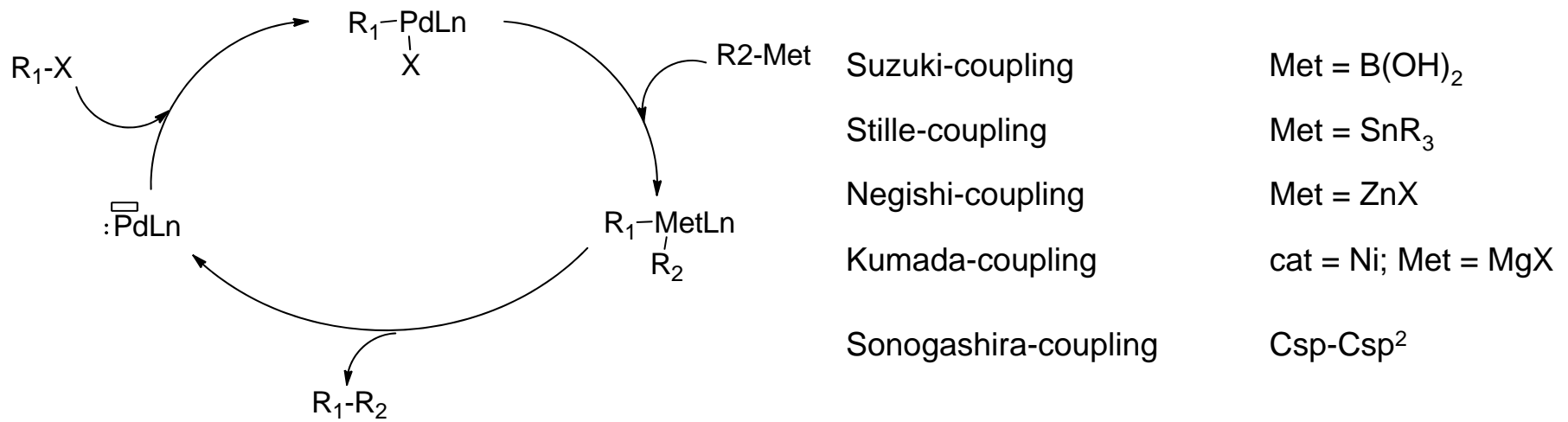
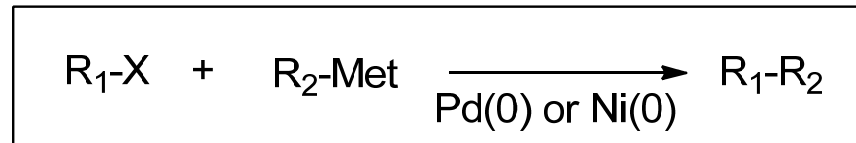
The method of T. Jeffery uses Bu₄NBr at 25 °C.

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

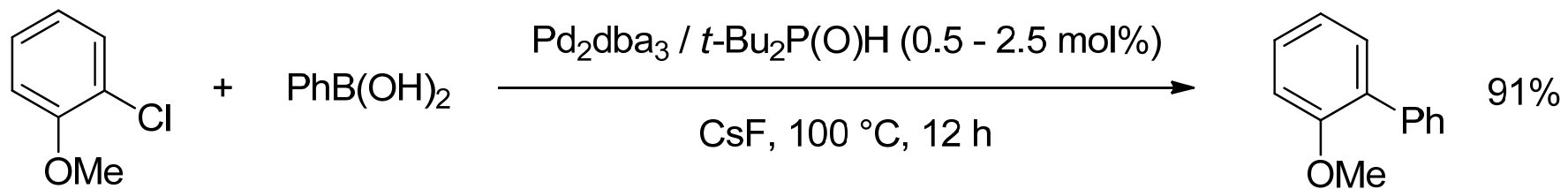
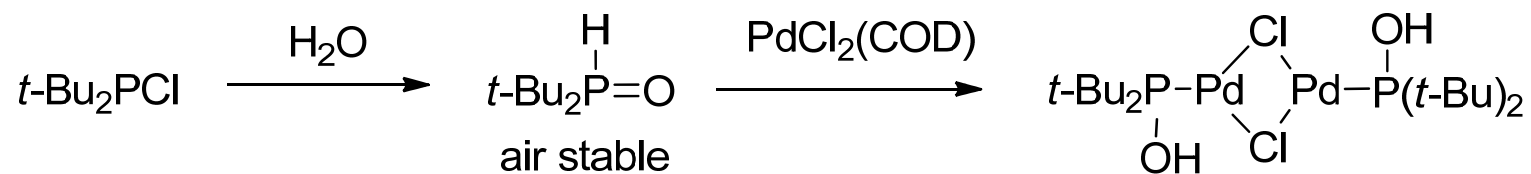


Palladium-catalyzed cross-coupling

Cross-coupling using Pd(0)-catalysts

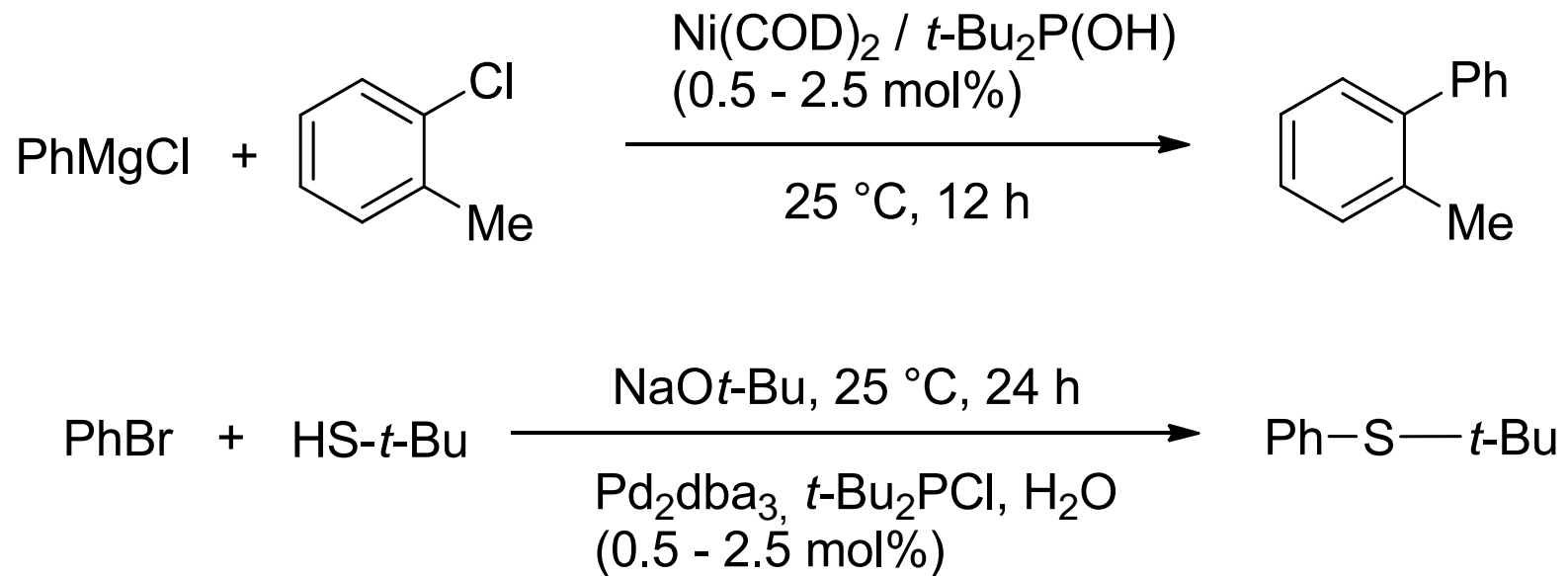


Palladium



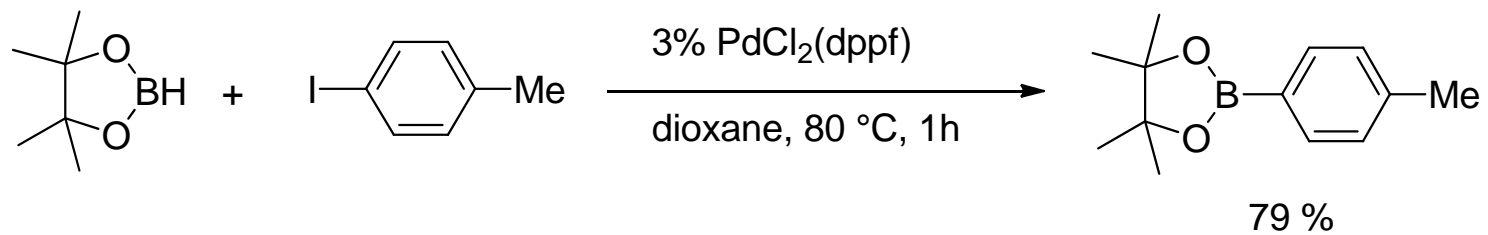
G. Y. Li, *Angew. Chem. Int. Ed.* **2001**, *40*, 1513.

Palladium

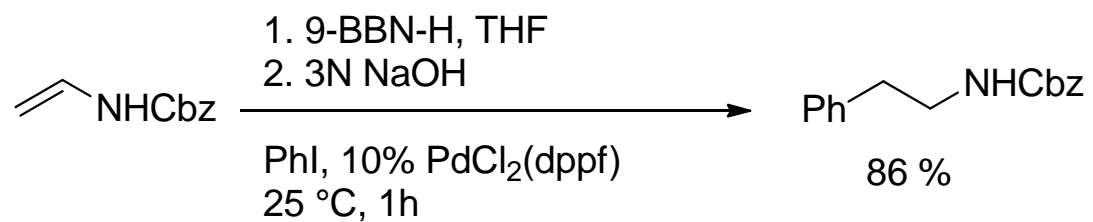


G. Y. Li, *Angew. Chem. Int. Ed.* **2001**, *40*, 1513.

Palladium



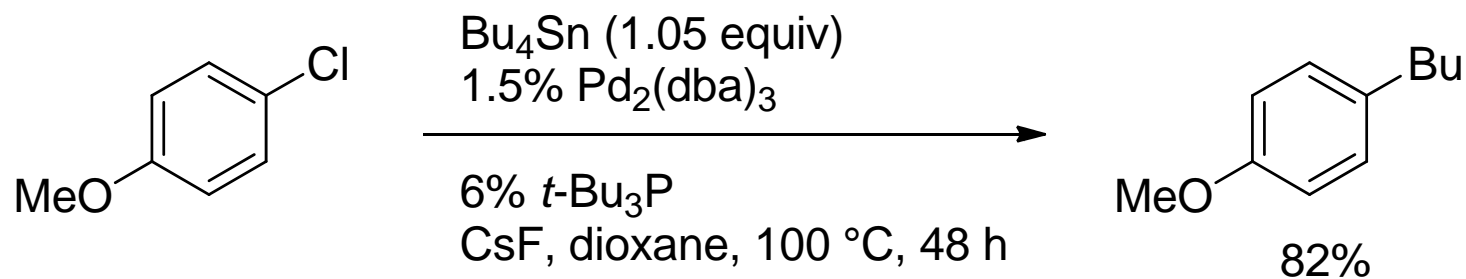
M. Murata, *J. Org. Chem.* **2000**, 65, 164.



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

Palladium

Stille cross-coupling



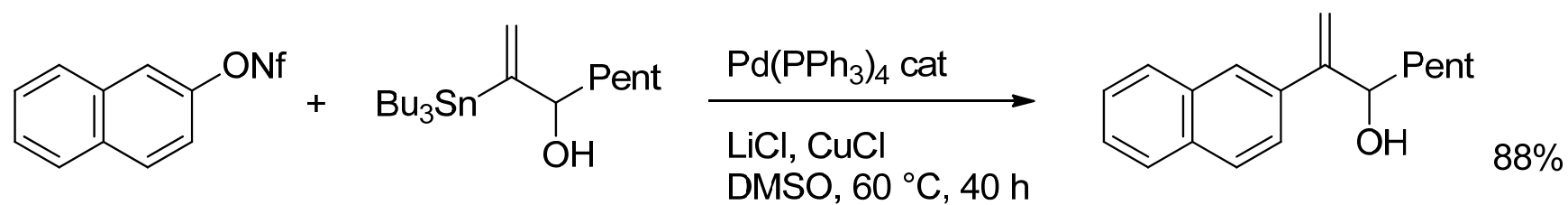
G. C. Fu, *Angew. Chem. Int. Ed.* **1999**, 38, 2411.

On the mechanism of the Stille cross-coupling:

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

Palladium

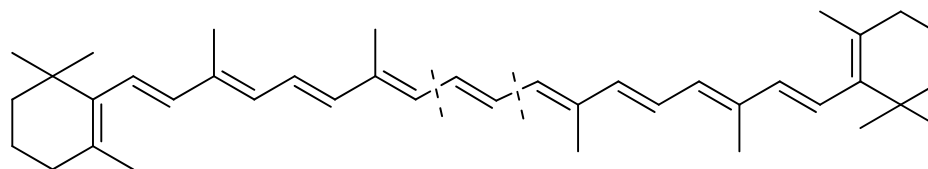
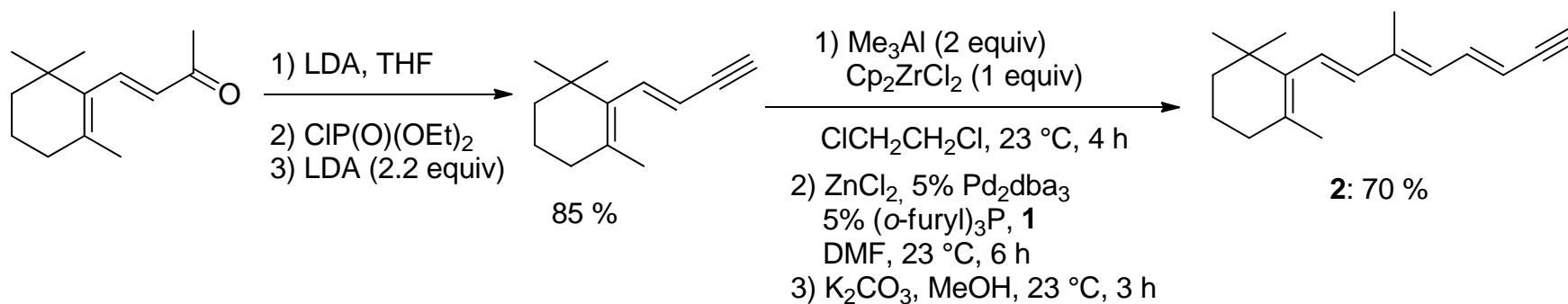
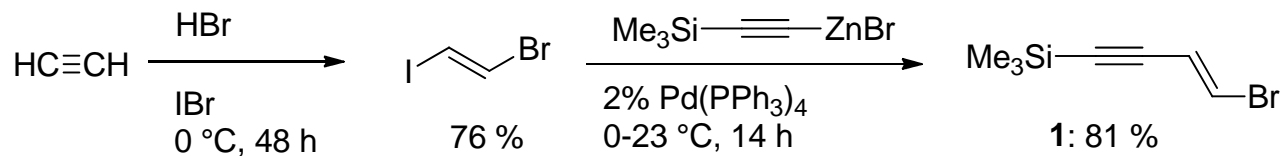
Cu-accelerated Stille-reaction



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

Negishi reactions

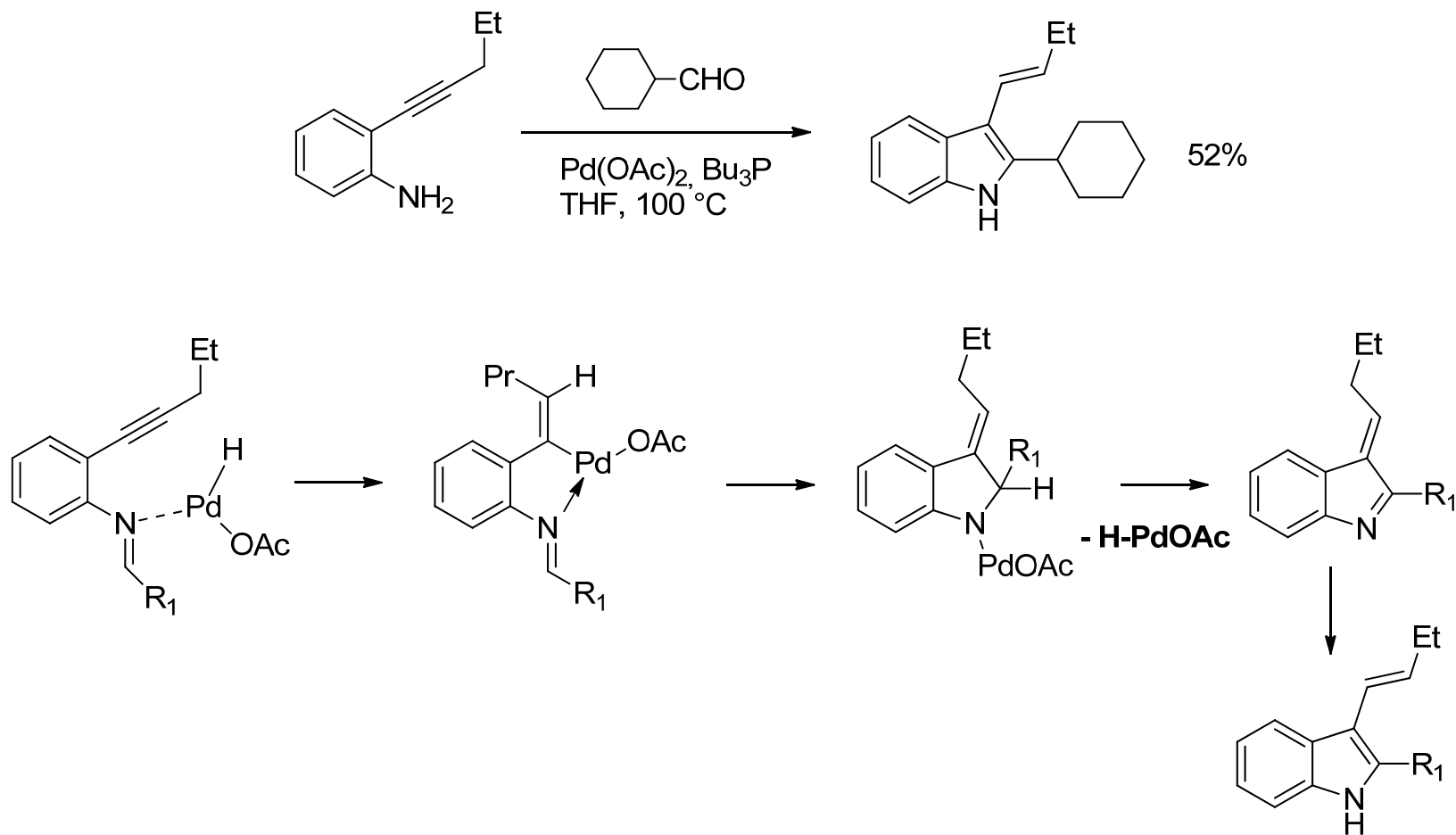
Synthesis of carotenoids *via* Zr-catalyzed carboalumination and Pd /Zn-catalyzed cross-couplings:



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

Palladium

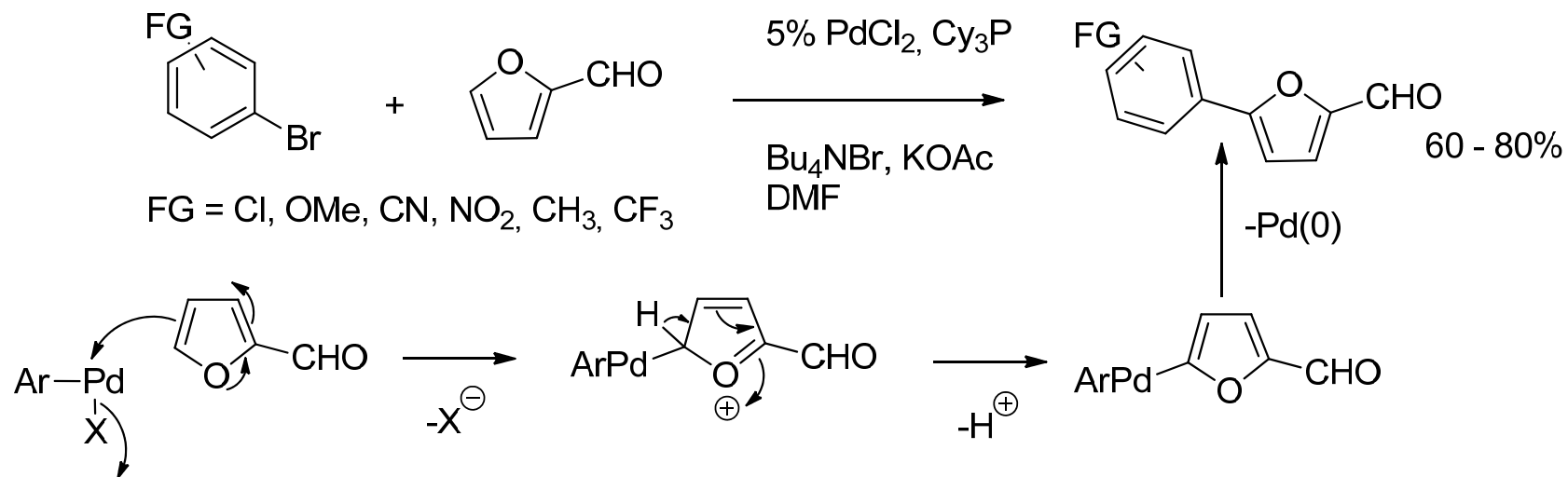
Example of an indole synthesis *via* an intramolecular cyclization of alkynes and imines using a Pd-catalyst:



H. Yamamoto, *J. Am. Chem. Soc.* **2000**, 122, 5662.

Palladium

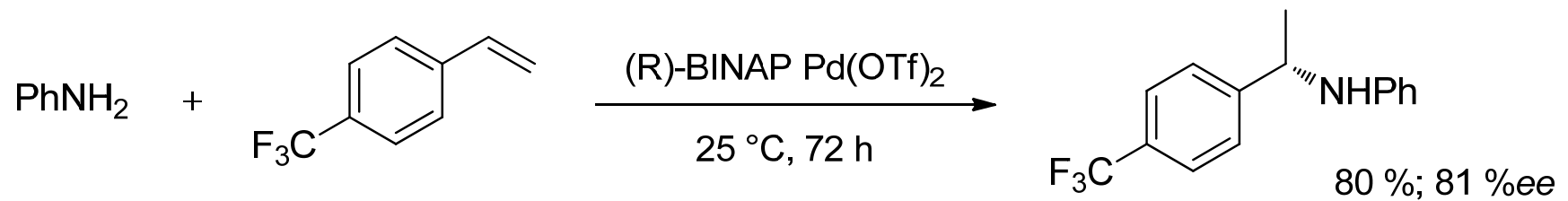
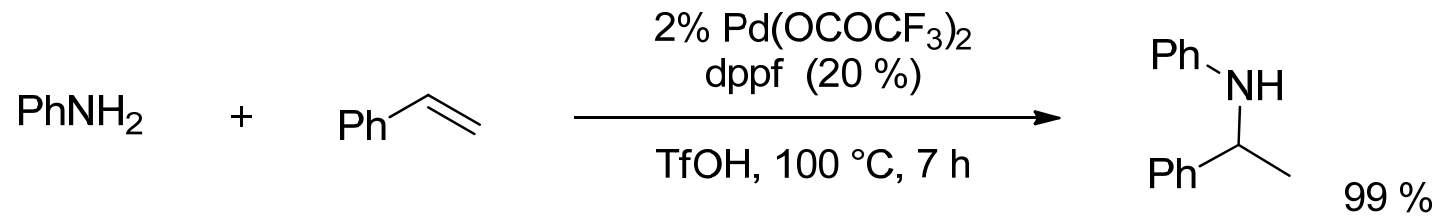
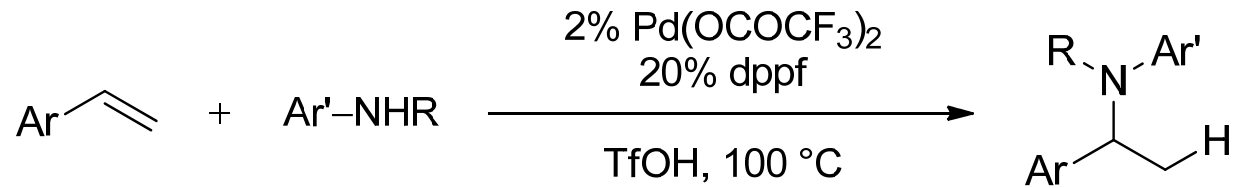
Regioselective Pd-catalyzed arylation of 2-furaldehyde using a C-H activation



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

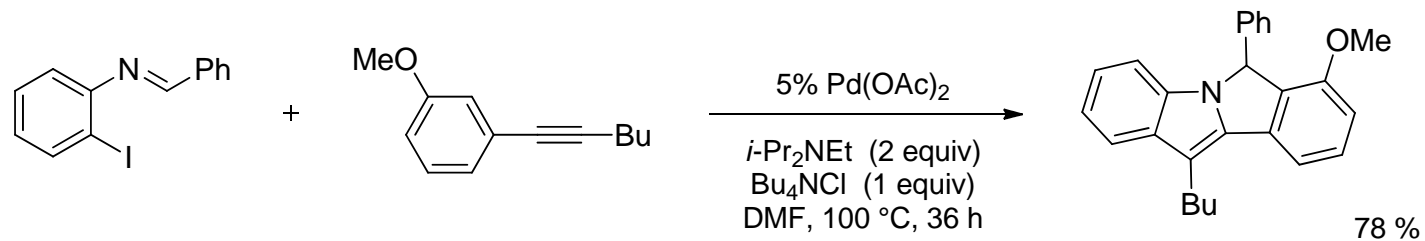
Palladium

Pd - catalyzed hydroamination of vinylarenes

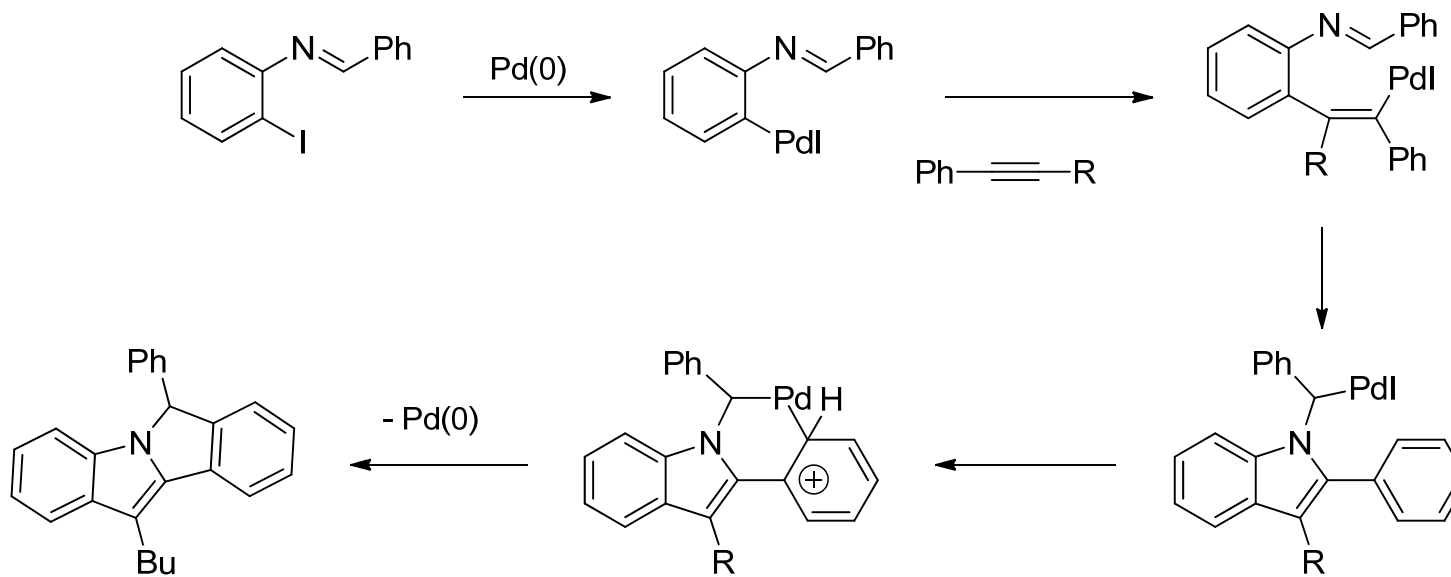


Palladium

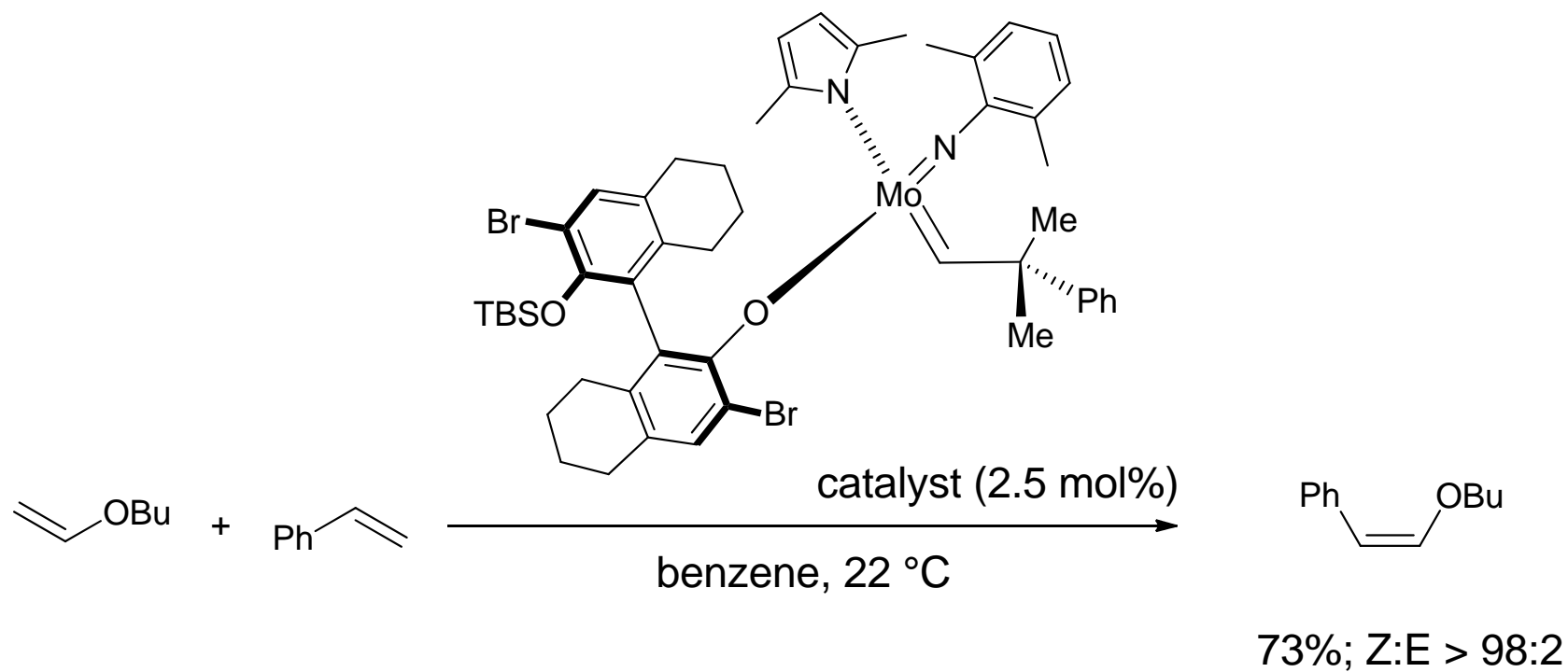
Pd-catalyzed heterocycle synthesis



Mechanism



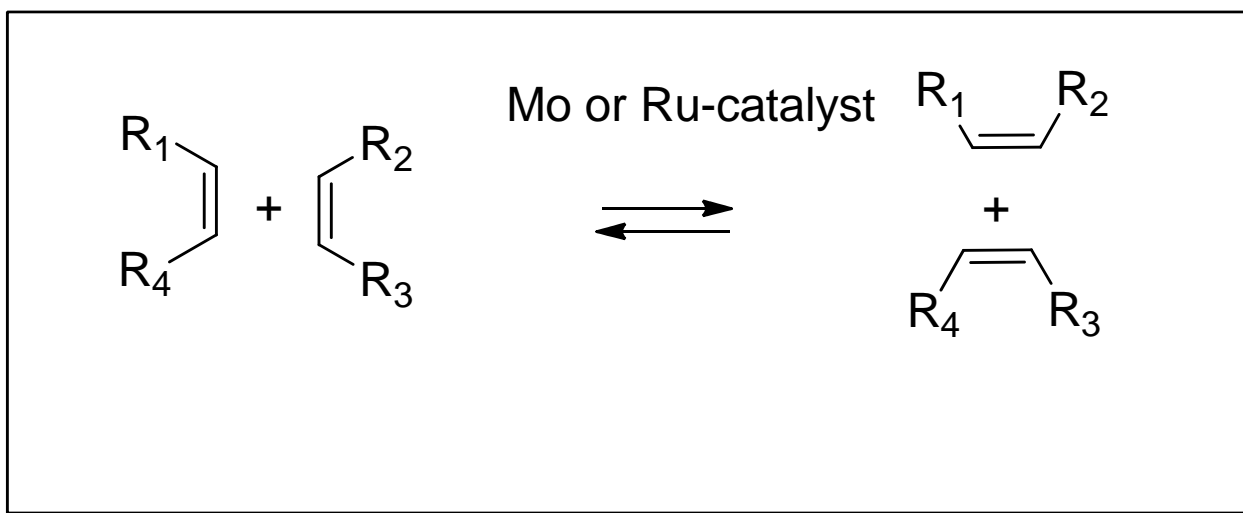
State of the art



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

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

Olefin metathesis



Reviews:

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

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

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

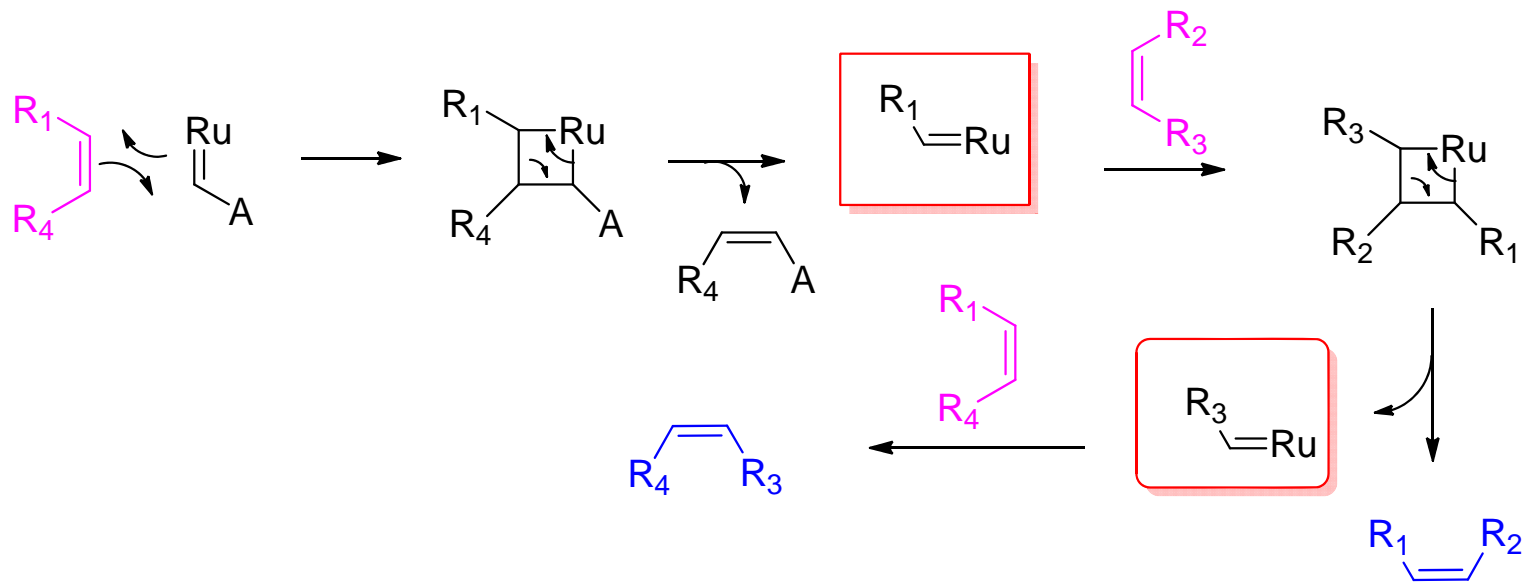
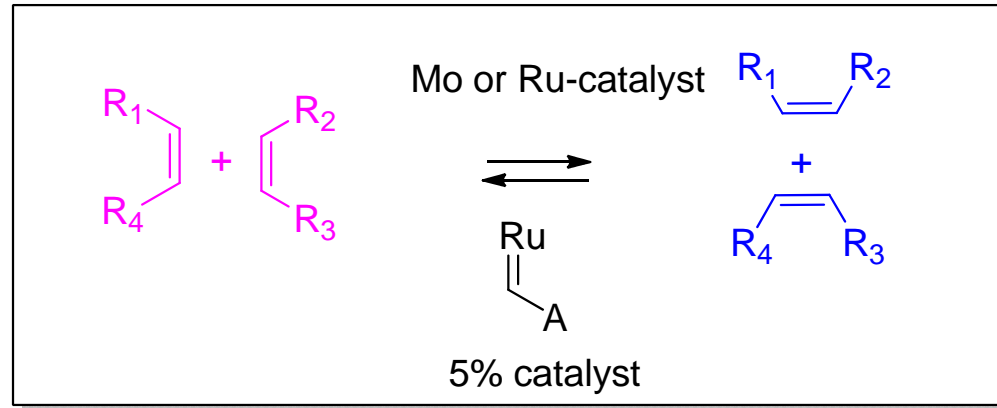
S. Blechert, *Angew. Chem.* **1997**, 109, 2124.

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

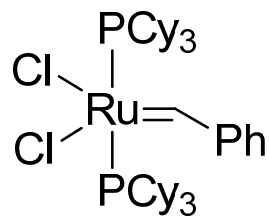
E.M. Carreira, *Synthesis* **2000**, 857.

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

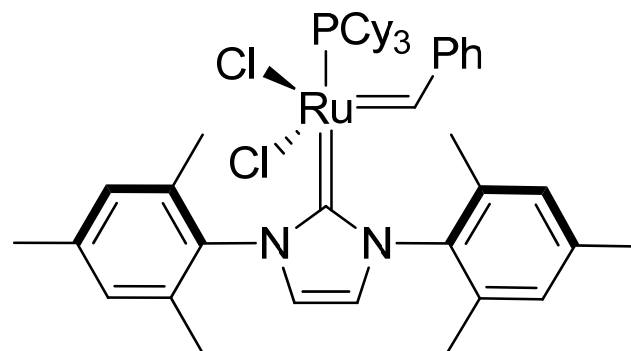
Olefin metathesis mechanism



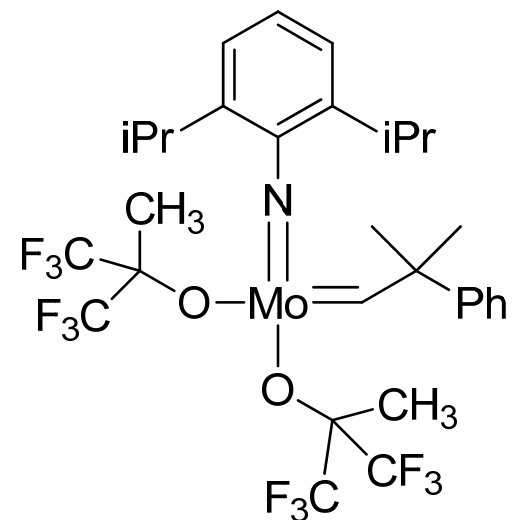
Olefin metathesis



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

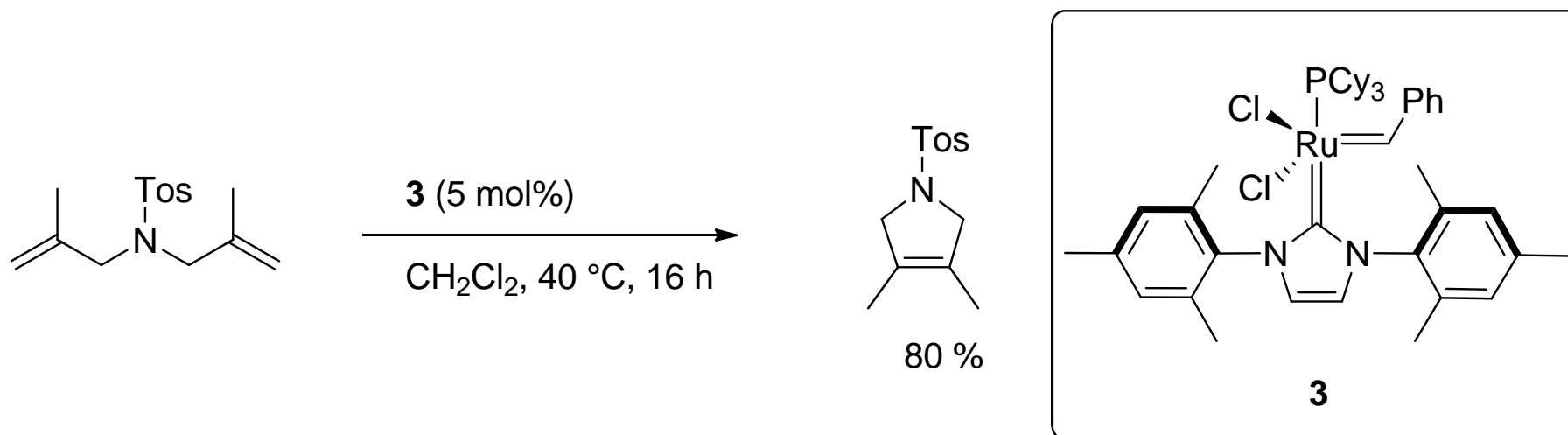


2: Grubbs-catalyst
second generation
US Patent No. 6,111,121
and 7,329,758



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

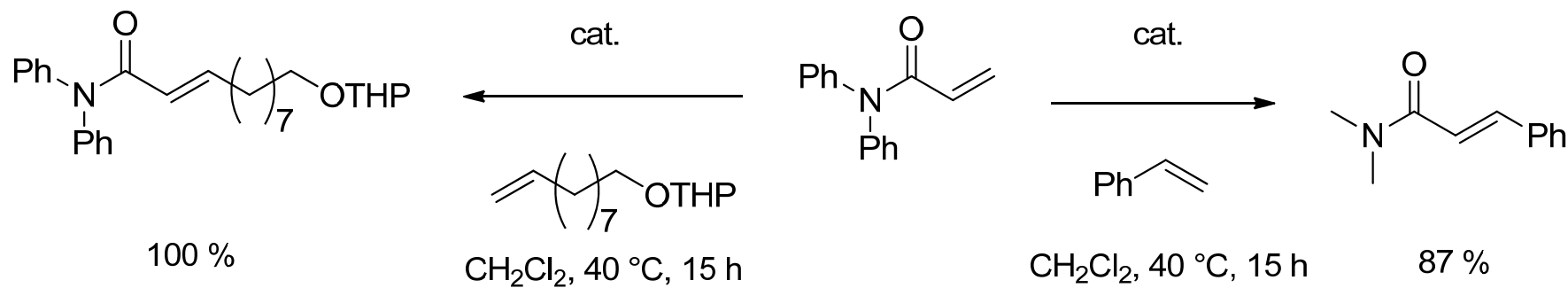
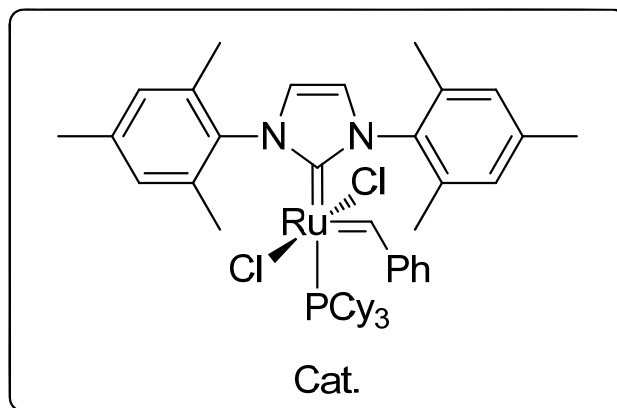
Olefin metathesis



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

Olefin metathesis

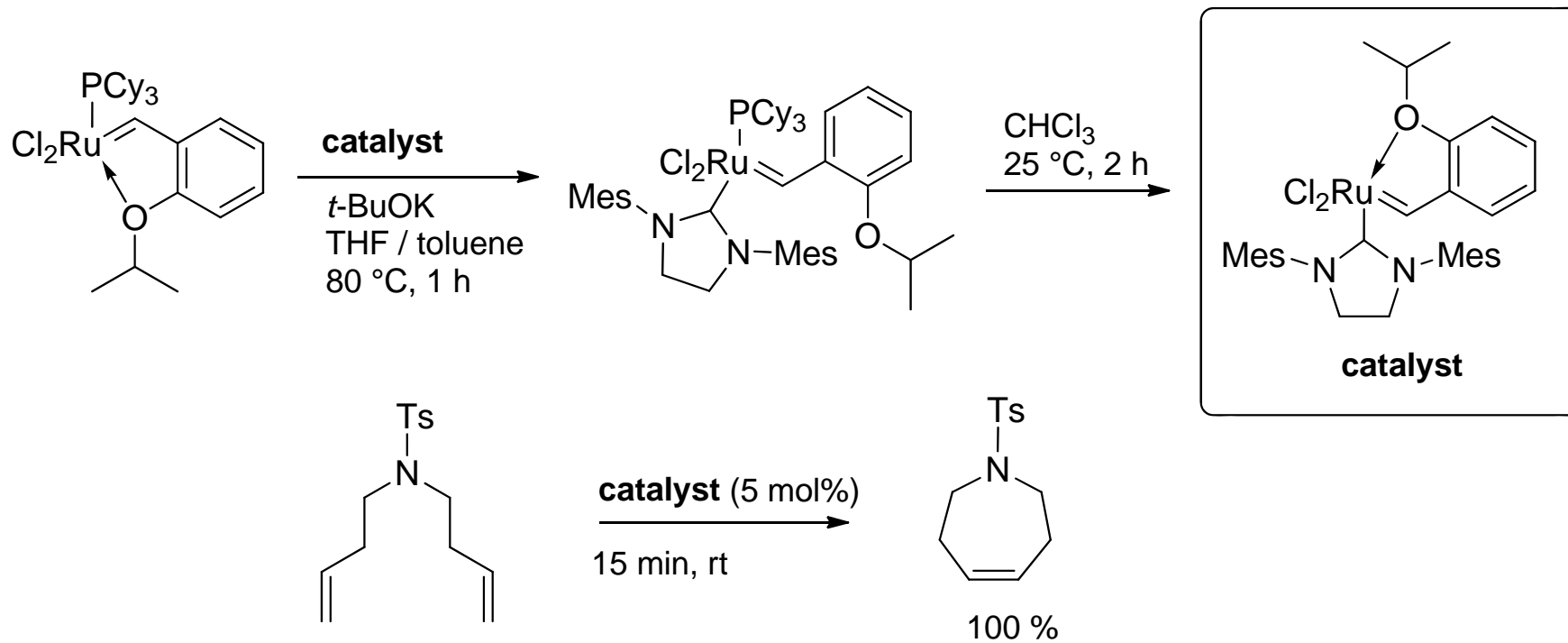
Synthesis of α,β -unsaturated amides by olefin cross-metathesis



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

Olefin metathesis

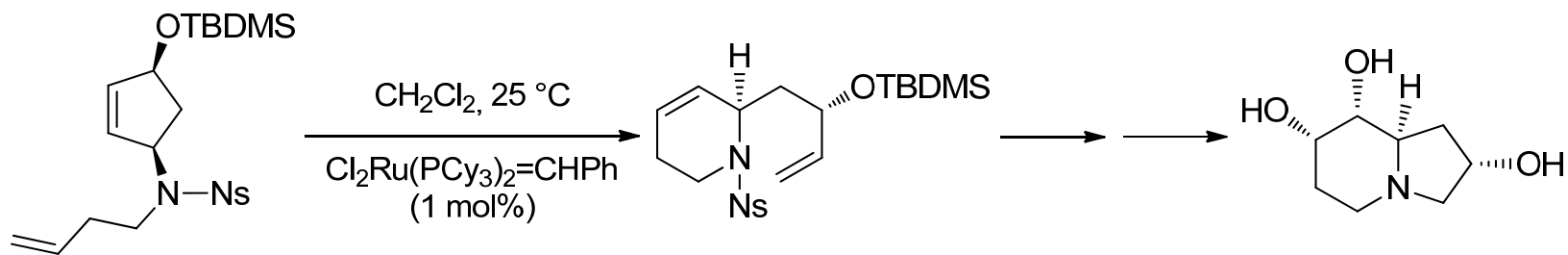
New phosphine-free metathesis catalyst



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

Application to the synthesis of natural products

Synthesis of aza sugars

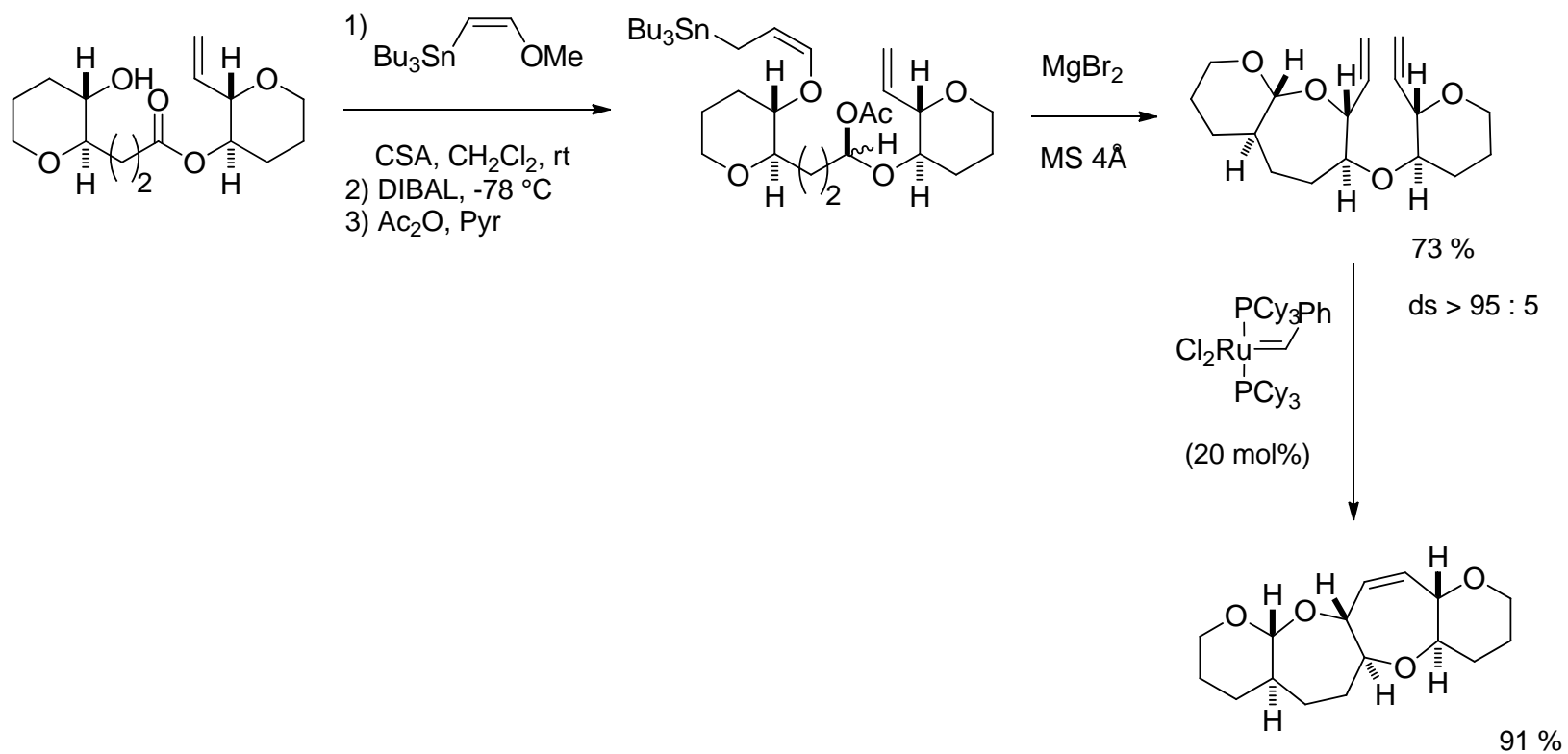


Ns = (o-NO₂)C₆H₄SO₂⁻

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

Olefin metathesis

Synthesis of complex ring-systems *via* metathesis



Olefin metathesis

Cross-/ self-metathesis with allylsilanes



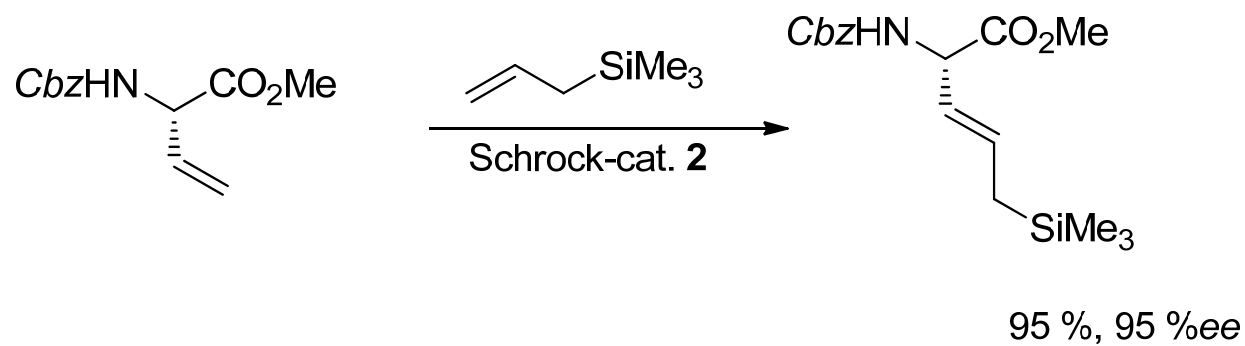
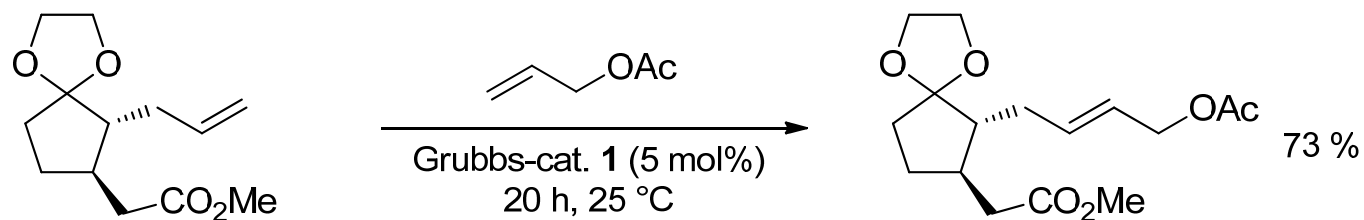
S. Blechert, *Chem. Eur. J.* **1997**, 3, 441.

Cross-metathesis with allylic silyl ethers:
A.G.M. Barrett, *Chem. Commun.* **1996**, 2229 and 2231

Cross-metathesis with fluorinated olefins:
S. Blechert, *Chem. Commun.* **2001**, 1692

Olefin metathesis

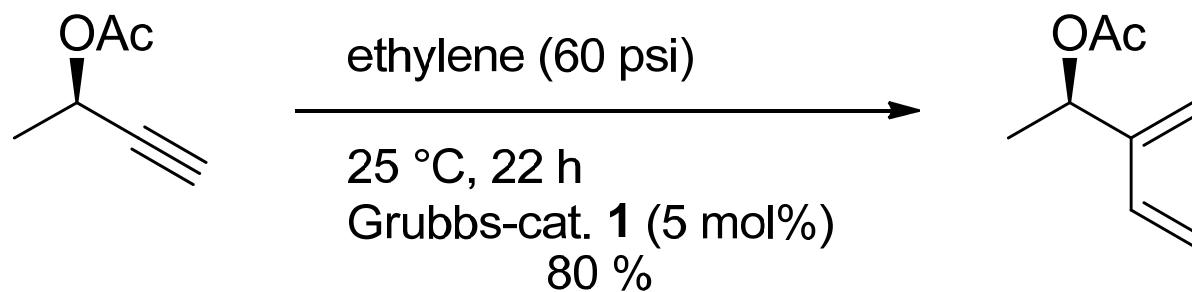
Synthesis of jasmonic acid derivatives



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

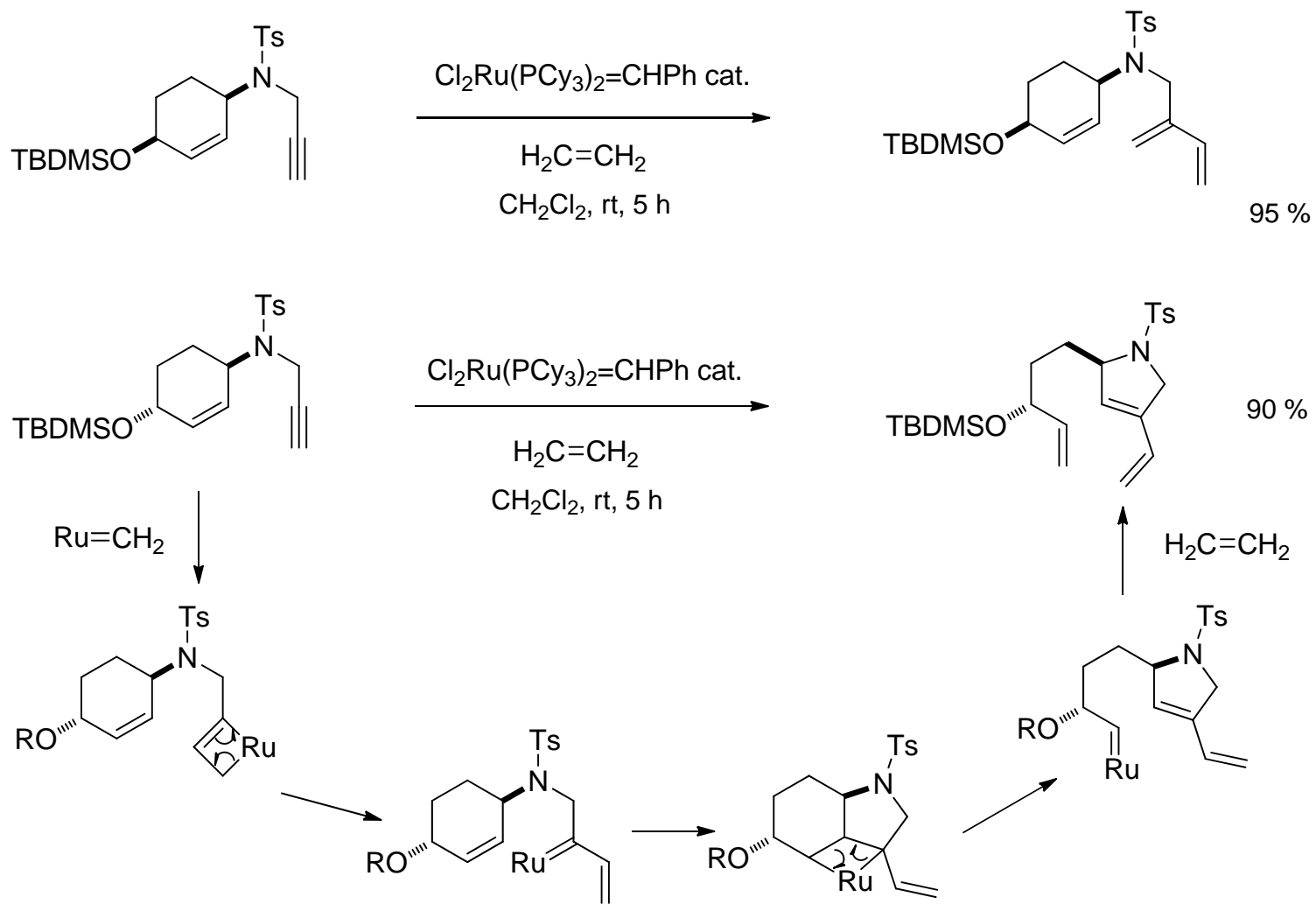
Olefin metathesis

Cross-metathesis of alkynes with ethylene



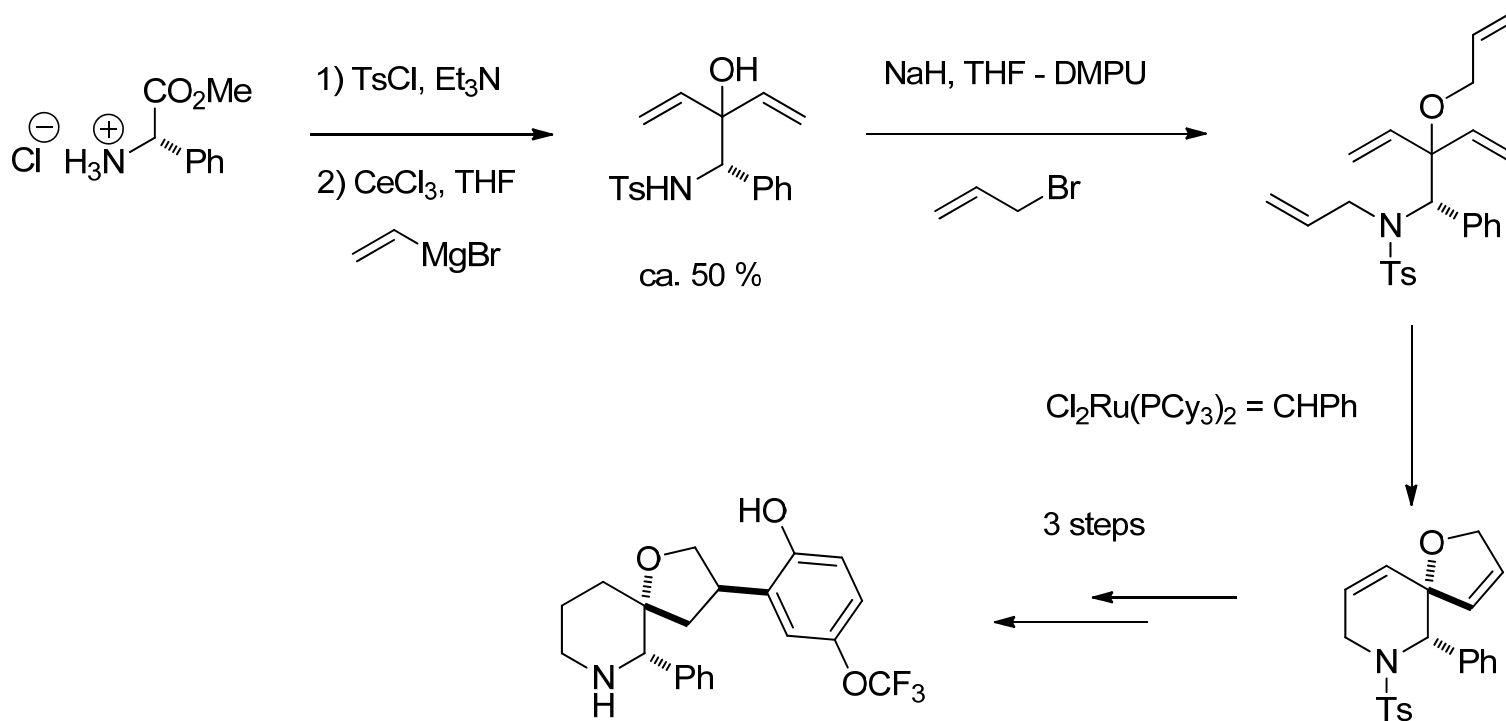
Olefin metathesis

Ru-catalyzed Ring-Opening and -Closing Enyne Metathesis

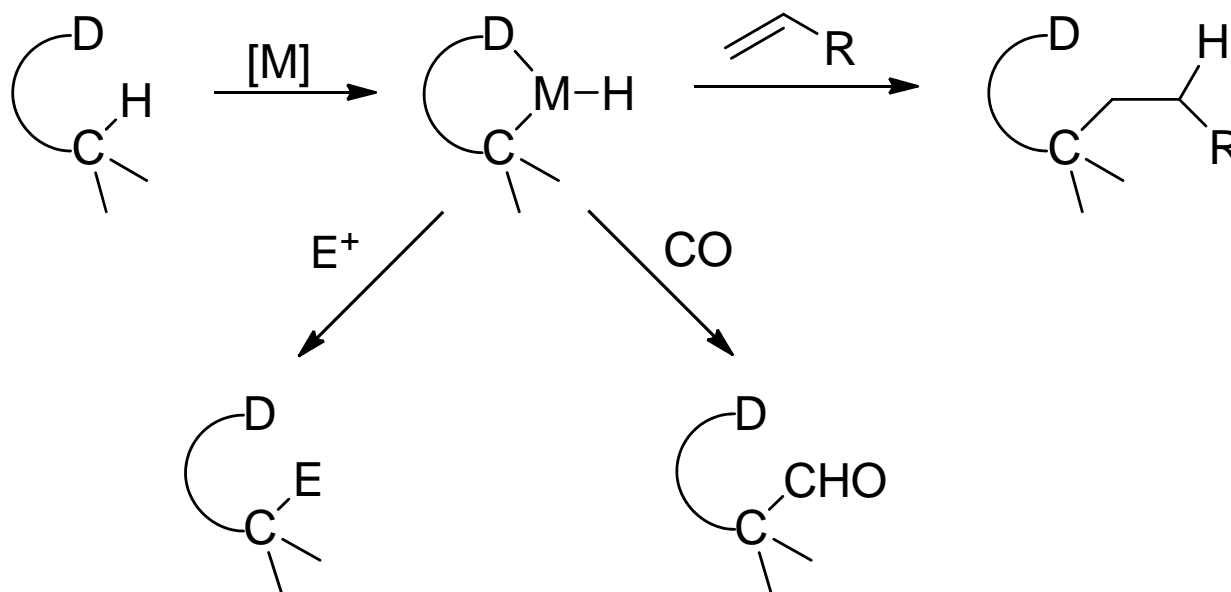


Olefin metathesis

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

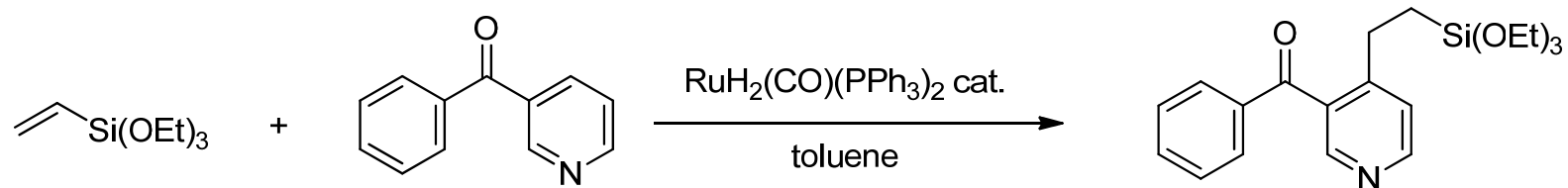
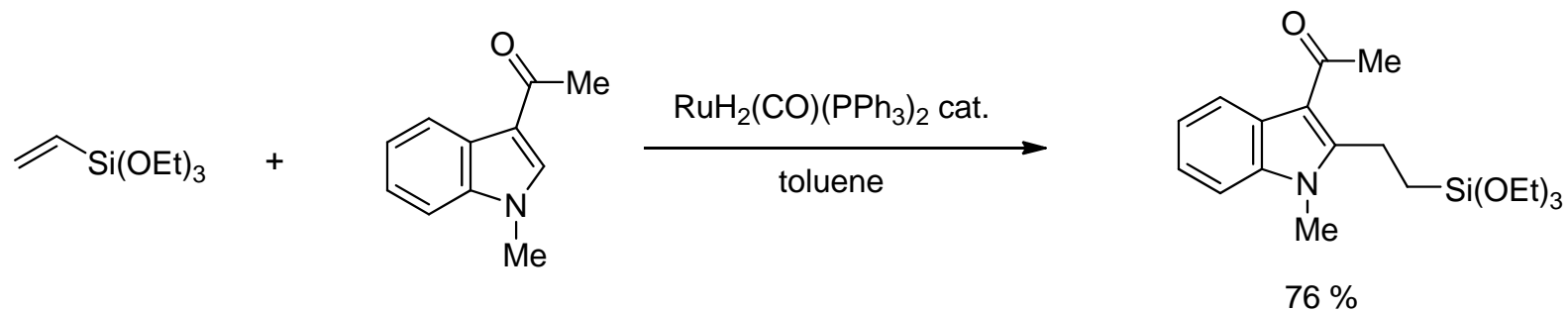


New C-H activation reactions



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

The Murai-reaction



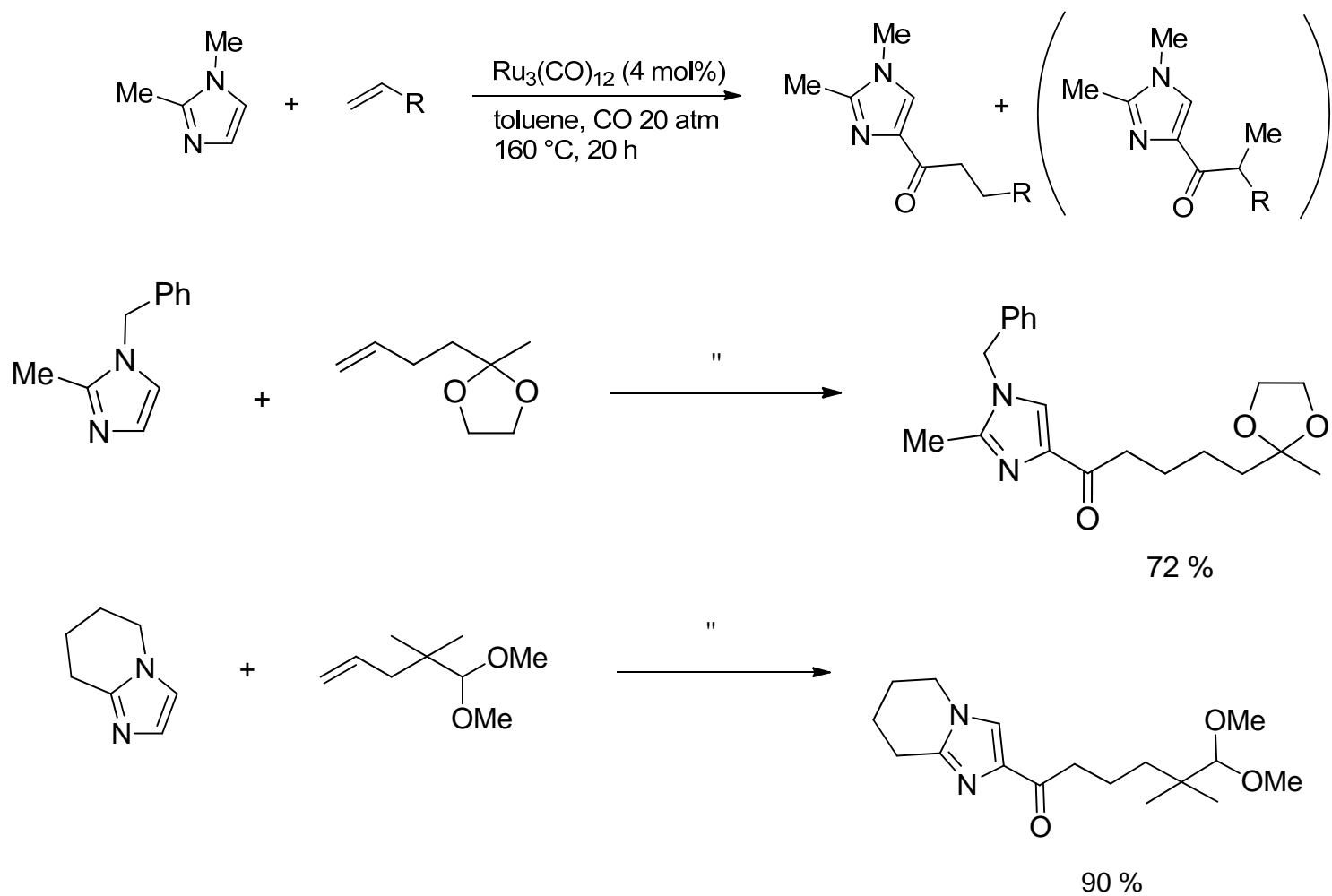
R. Grigg, *Tetrahedron Lett.* **1997**, 38, 5737

S. Murai, *Nature*, **1993**, 366, 529

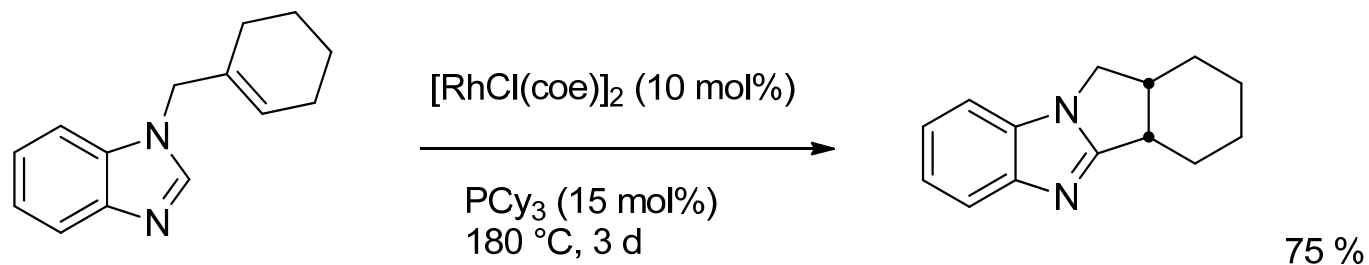
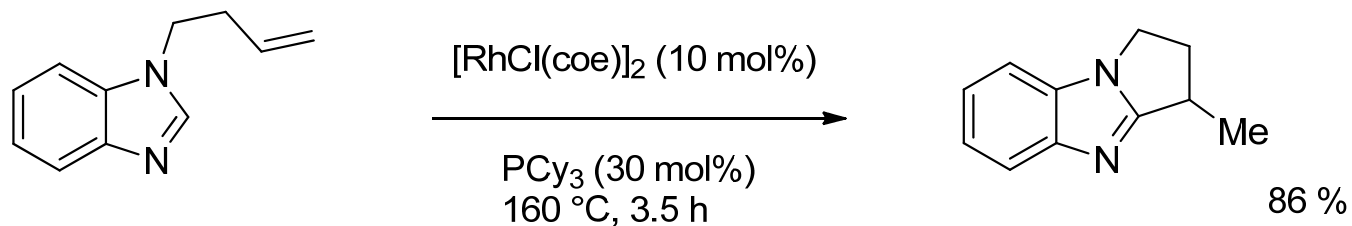
S. Murai, *J. Organomet. Chem.* **1995**, 504, 151

The Murai-reaction

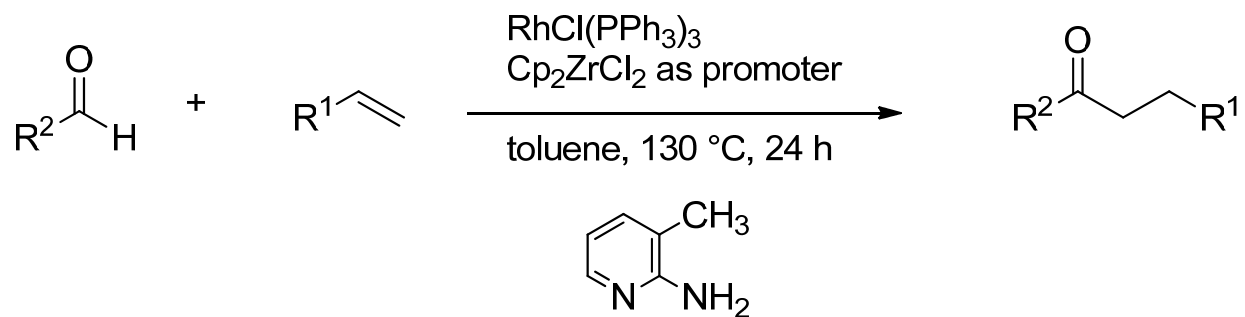
Ru-mediated synthesis of 4-acylated imidazoles *via* C-H-activation



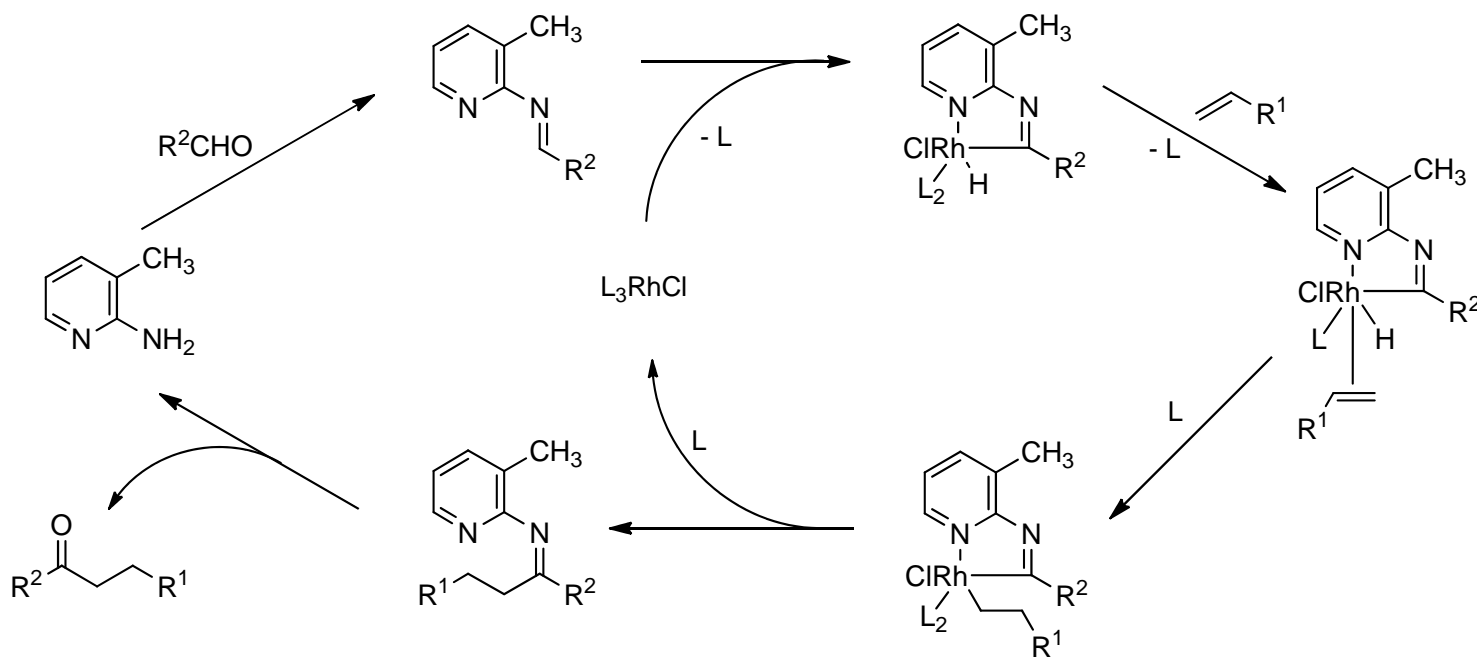
Annulation of heterocycles *via* a Rh-catalyzed C-H-activation



The catalytic hydroacylation of alkenes



Mechanism:

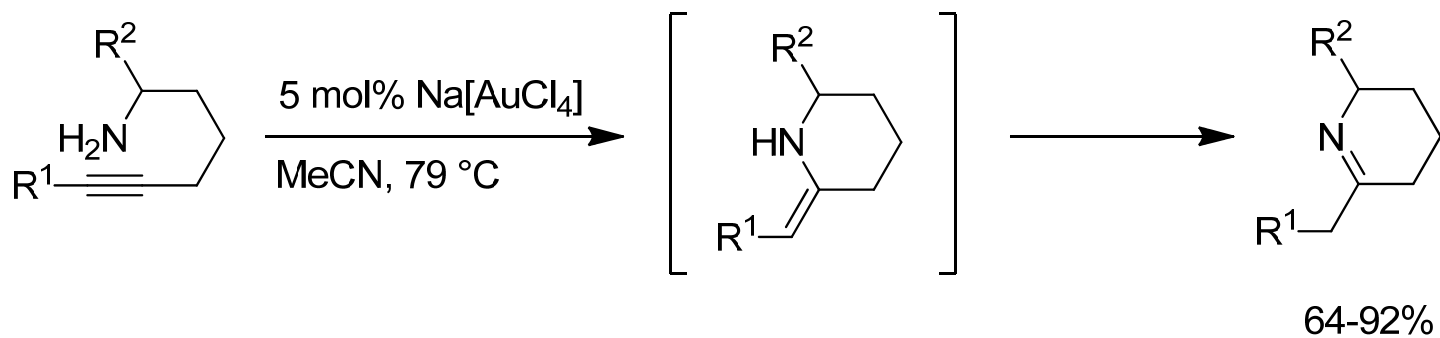
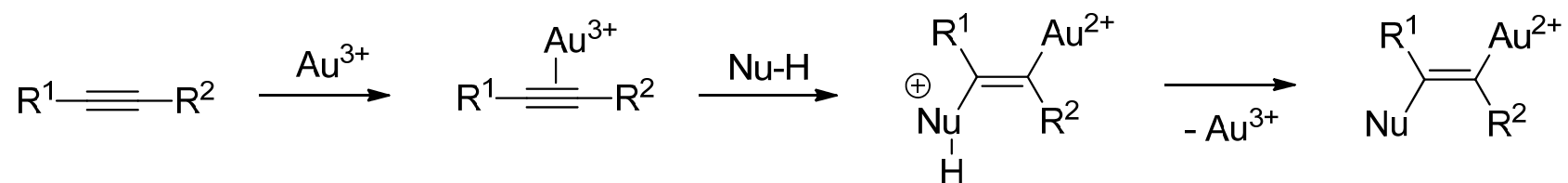


Review: C.-H. Jun, *Synlett*, **1999**, 1

C.-H. Jun, *Org. Lett.* **1999**, 1, 887; *Tetrahedron Lett.* **1997**, 38, 6673; *J. Org. Chem.* **1997**, 62, 1200

Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds

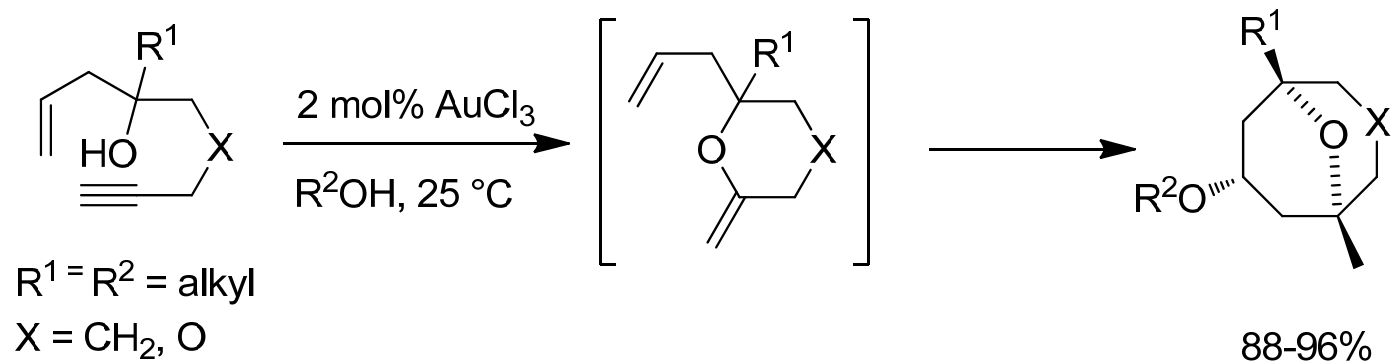


For a review see: A. S. Hashmi, *Chem. Rev.* **2007**, *107*, 3180

Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds:

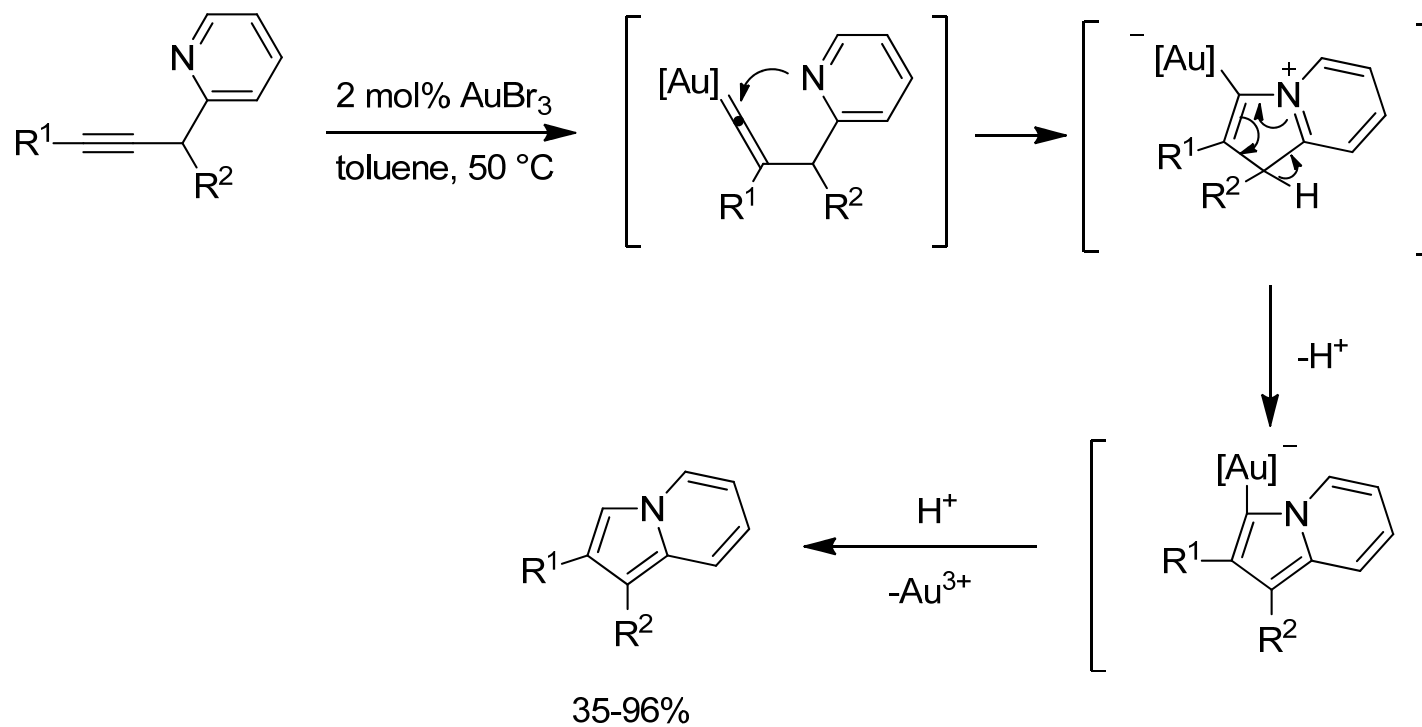
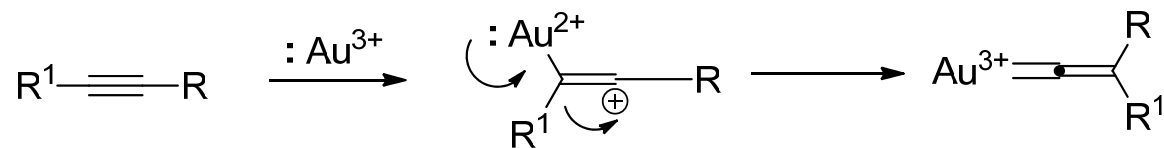
Au³⁺-catalyzed cyclization followed by a Prins type cyclization



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

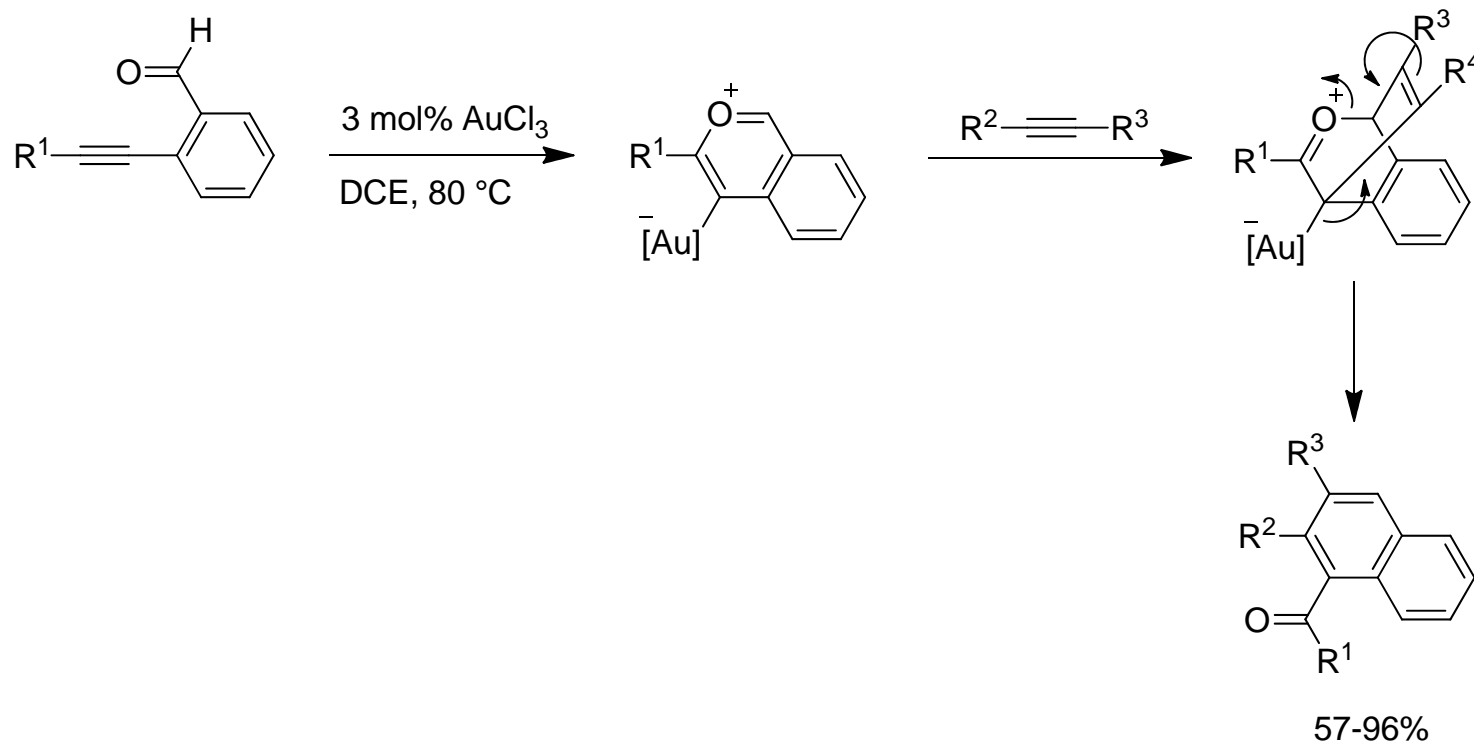
Gold-catalyzed organic reactions

Gold(III)-triggered rearrangements



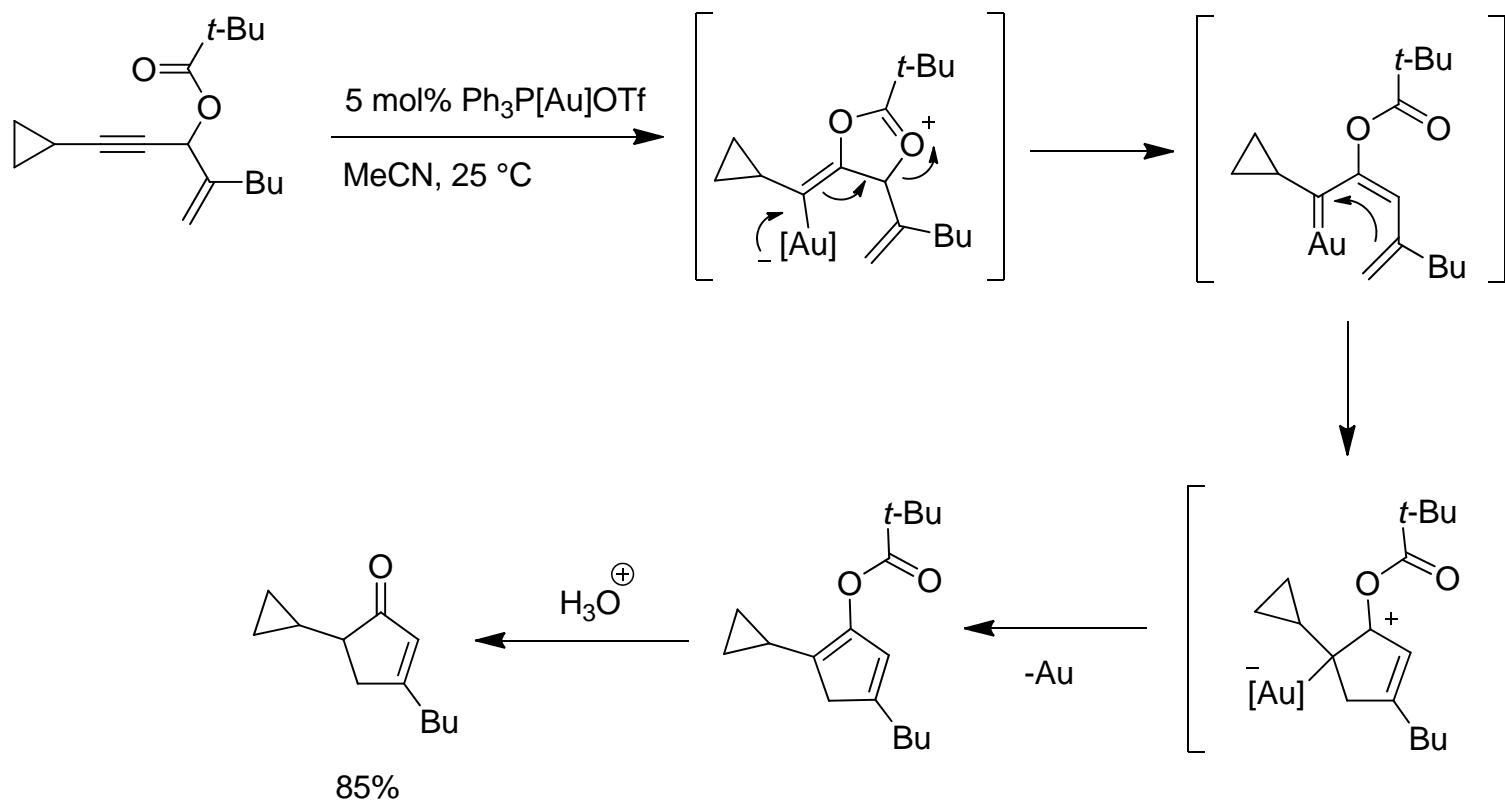
Gold-catalyzed organic reactions

Au³⁺-initiated cycloadditions



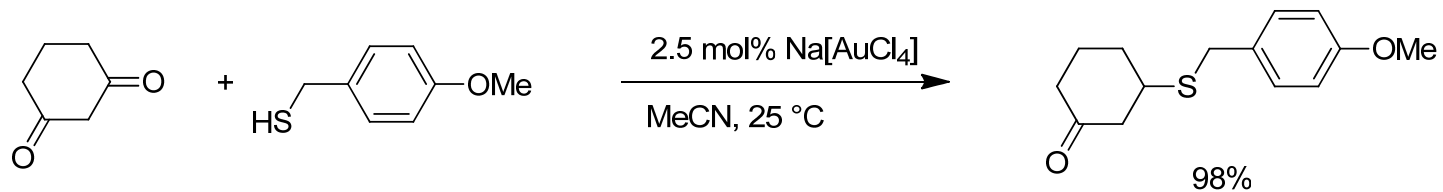
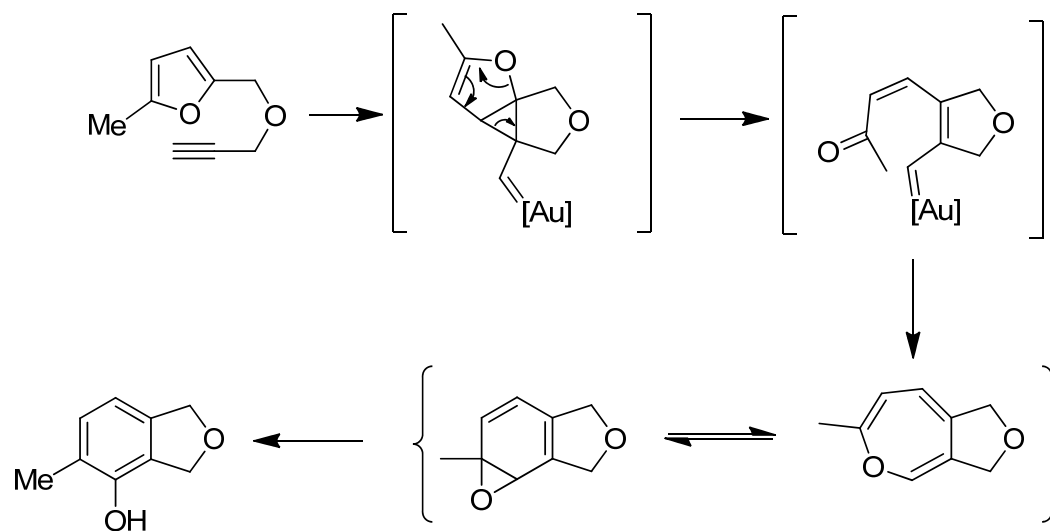
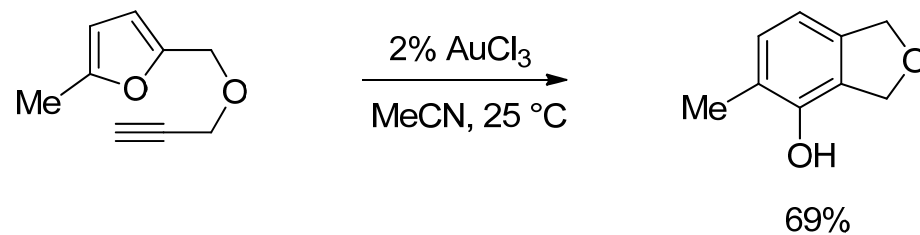
Gold-catalyzed organic reactions

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



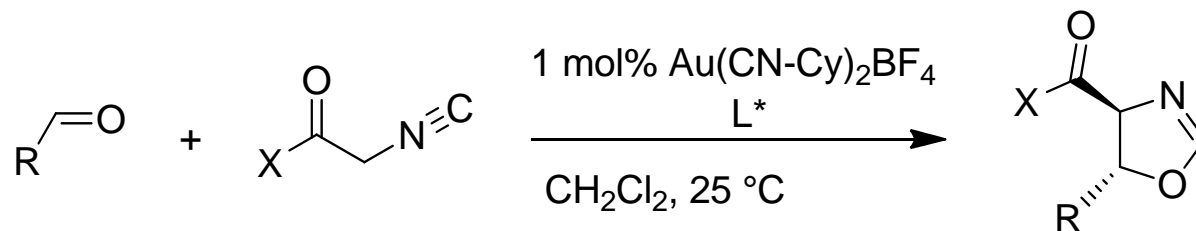
Gold-catalyzed organic reactions

Intramolecular phenol synthesis



Gold-catalyzed organic reactions

Asymmetric aldol reaction



86-97%

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

