Organic Chemistry IV

Organometallic Chemistry for Organic Synthesis

Prof. Paul Knochel
LMU
2012

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OCIV

Prüfung:
Freitag 20. Juli 9-11 Uhr
Wieland HS

Wiederholungsklausur:
Donnerstag 13. September 14-16 Uhr
Baeyer HS

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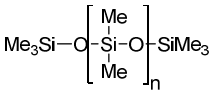
Recommended Literature

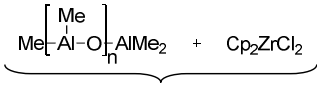
1. **F. A. Carey, R. J. Sundberg, Advanced Organic Chemistry**, Fifth Edition Part A and Part B, Springer, 2008, ISBN-13: 978-0-387-68346-1
2. **R. Brückner, Organic Mechanisms**, Springer, 2010, ISBN: 978-3-642-03650-7
3. **L. Kürti, B. Czako, Strategic applications of named reactions in organic synthesis**, 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



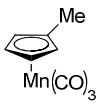
Silicone

Et_4Pb



Kaminsky catalyst
n=5-20 syndiotacticity of polypropylene

BuLi



Industrial production

Industrial annual production of various organometallics

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

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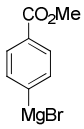
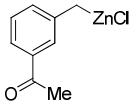
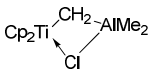
Organometallic reagents and catalysts for the organic synthesis

organometallic reagents:

BuLi



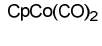


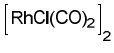


Tebbe reagent

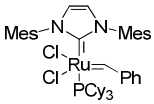
Schwarz reagent

organometallic catalysts:

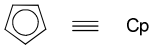




Wilkinson's catalyst



Grubbs II catalyst



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State of the art

80%; dr: 95 : 5
Z:E > 98:2

A. H. Hoveyda, *J. Am. Chem. Soc*. **2009**, *131*, 3844
O. Eisenstein, C. Copéret *J. Am. Chem. Soc*. **2007**, *129*, 8207

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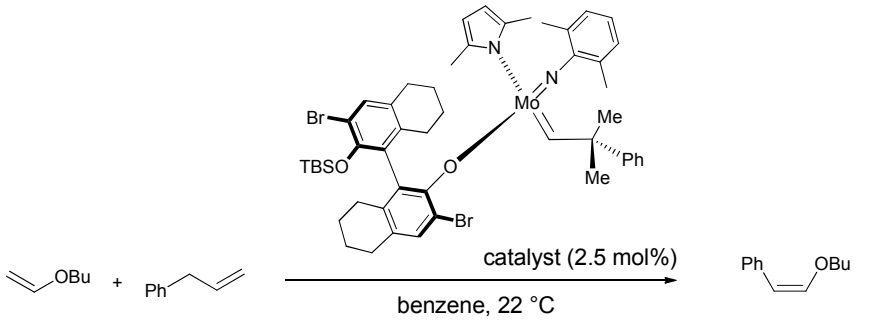
State of the art



73%; Z:E > 98:2

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

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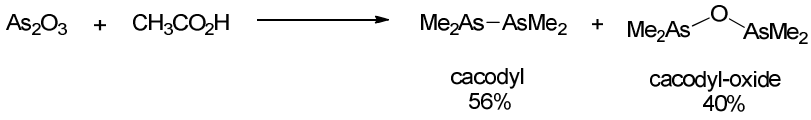
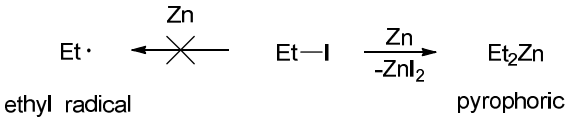
Historic point of view

1757 - Louis Cadet de Gassicourt (parisian apothecary)



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



Universität Marburg (1848)

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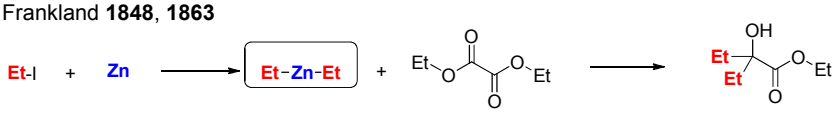
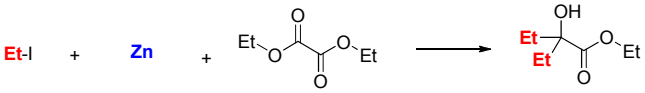
Organometallic chemistry of the XIX century

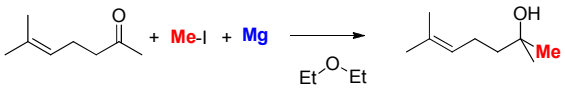
Frankland **1848**, **1863**



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



Barbier **1899**



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

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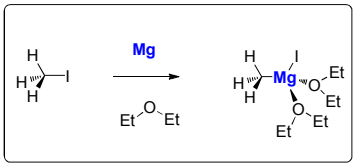
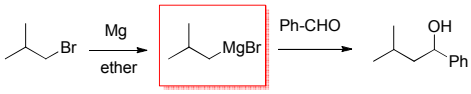
Organometallic chemistry of the XIX century

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





reactif de Grignard

V. Grignard

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

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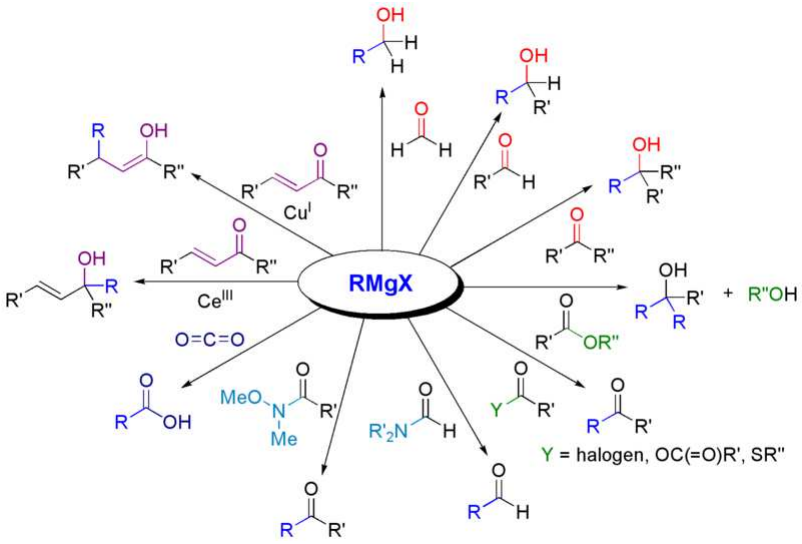
Reactivity of the Grignard reagents



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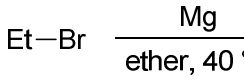
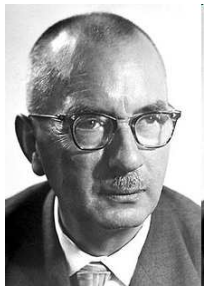
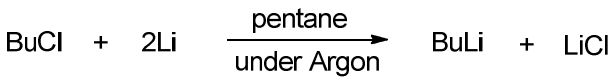
Historic point of view

Victor Grignard (1900)



Karl Ziegler (1919)





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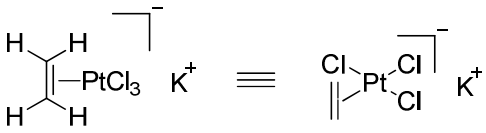
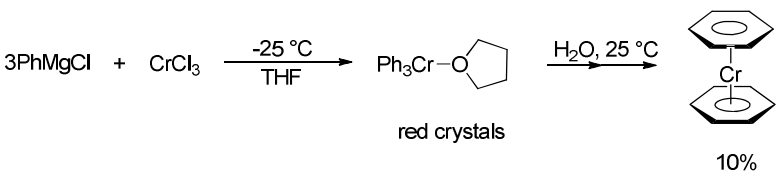
Historic point of view

first transition metal organometallics:

Zeise's Salz (1827)



Hein (1919)



red crystals

10%

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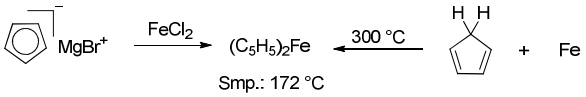
Historic point of view

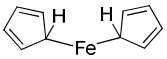
1951 : synthesis of ferrocene

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



G. Wilkinson

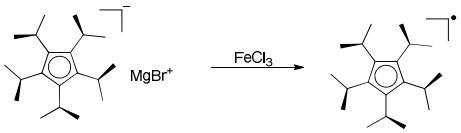
1952
structural proposal by Pauson



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

ferrocene

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



R. B. Woodward

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

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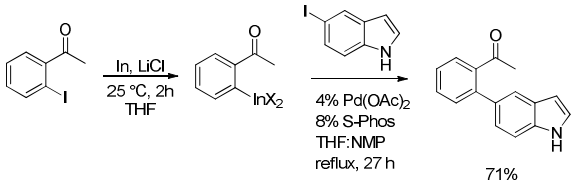
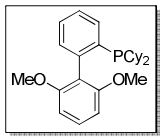
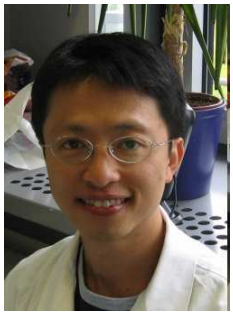
Goal of the lecture

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





S-Phos



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

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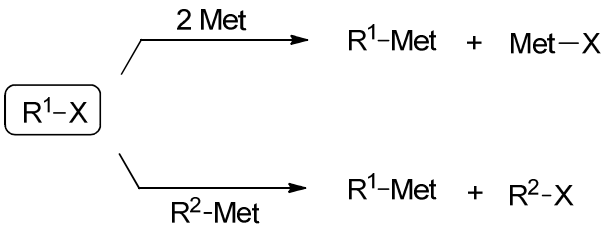
General synthetic methods for preparing organometallic reagents

classification according to starting materials

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



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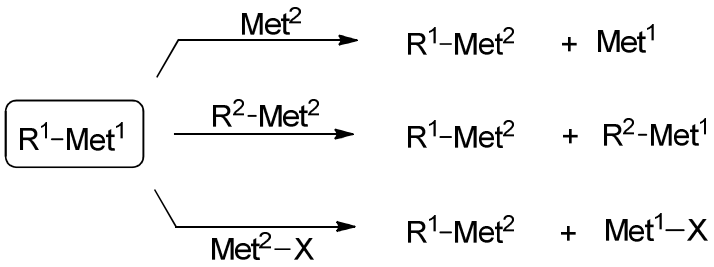
Classification according to starting materials

transmetalation



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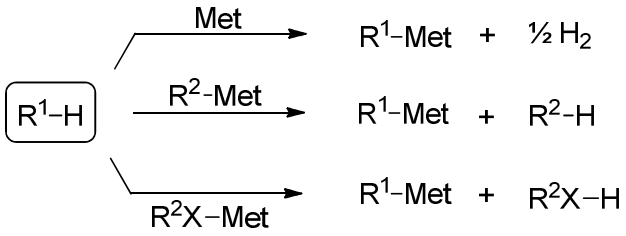
Classification according to starting materials

metalation



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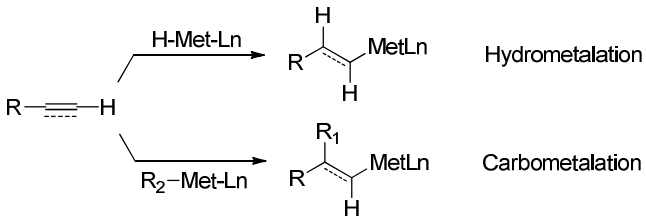
Classification according to starting materials

carbometalation and hydrometalation



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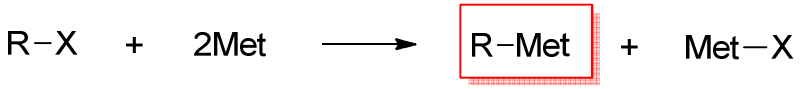
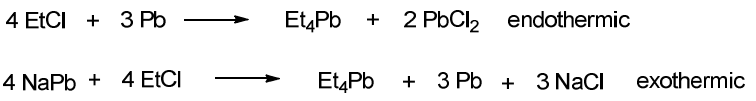
Synthesis starting from organic halides

direct synthesis - oxidative addition



driving force of the reaction:

$\triangle H = \Delta H[Met-X] + \Delta H[C-Met] - \Delta H[C-X]$ - lattice energy



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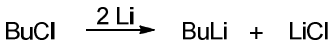
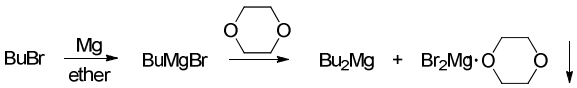
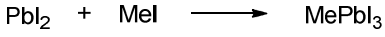
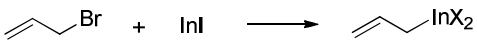
Direct Synthesis - Oxidative Addition

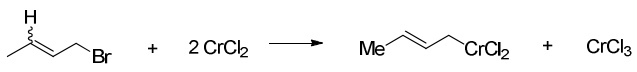
examples:











E/Z-mixture pure E-isomer

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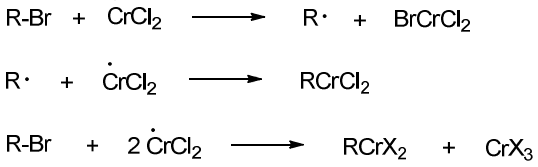
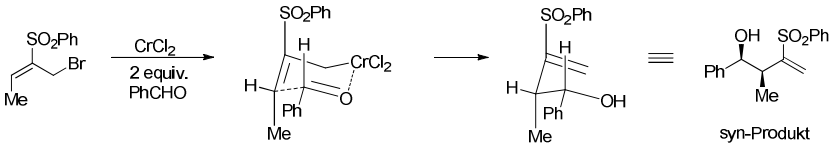
Direct Synthesis - Oxidative Addition

mechanism:



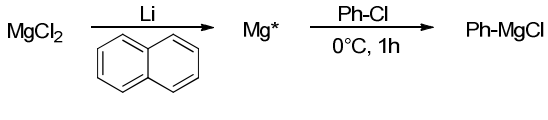


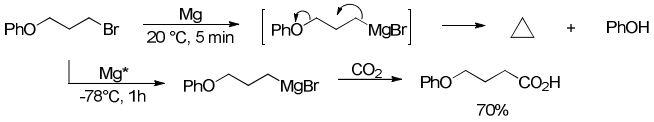
P. Knochel *Tetrahedron Lett*. **1986**, *27*, 5091

23

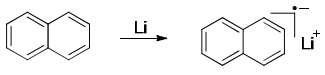
Rieke-approach

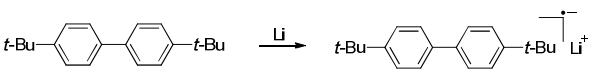
activation of the metal: R. D. Rieke, *Science* **1989**, *246*, 1260





soluble Li-sources:





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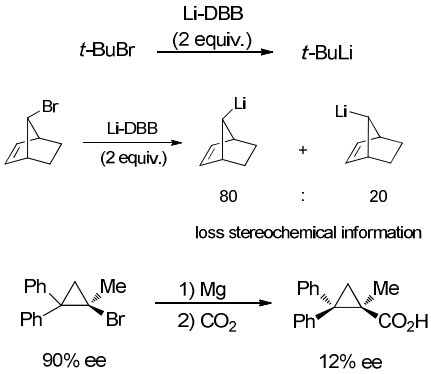
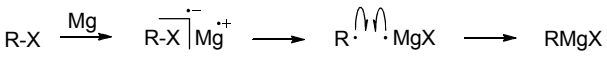
P.P. Freeman, L.L. Hutchinson *J. Org. Chem*. **1983**, *48*, 4705

Mechanism of the metal insertion



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



radical mechanism

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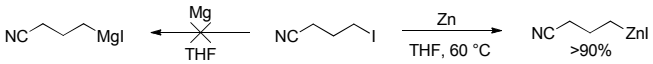
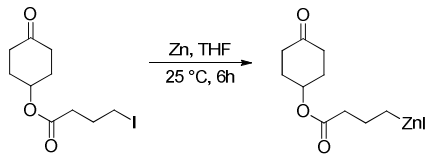
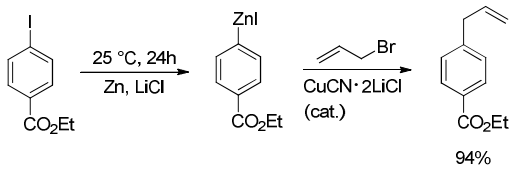
Preparation of functionalized organometallics





P. Knochel *J. Org. Chem*. **1988**, *53*, 2390
P. Knochel *Org. React*. **2001**, *58*, 417-731



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

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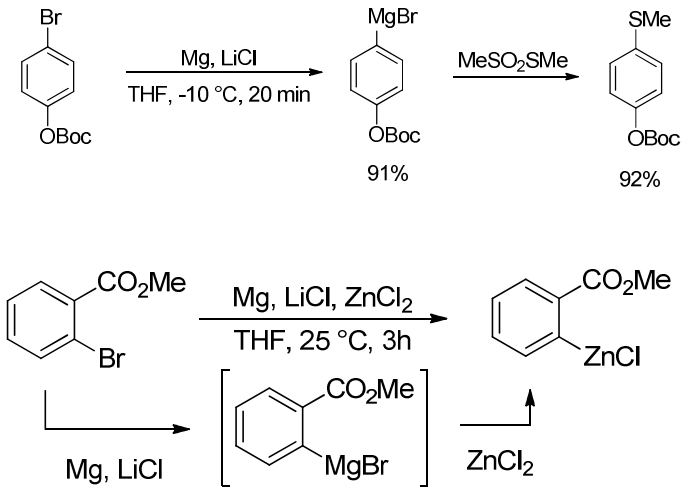
Preparation of functionalized organometallics



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

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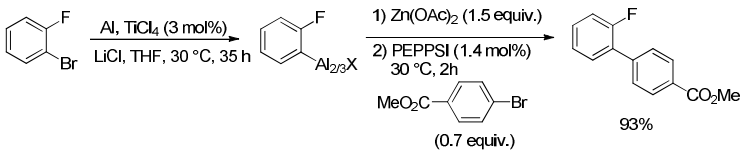
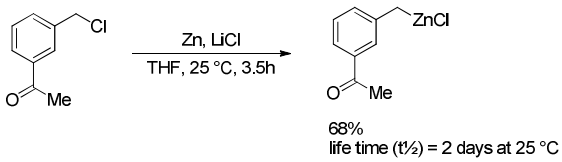
Preparation of functionalized organometallics

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



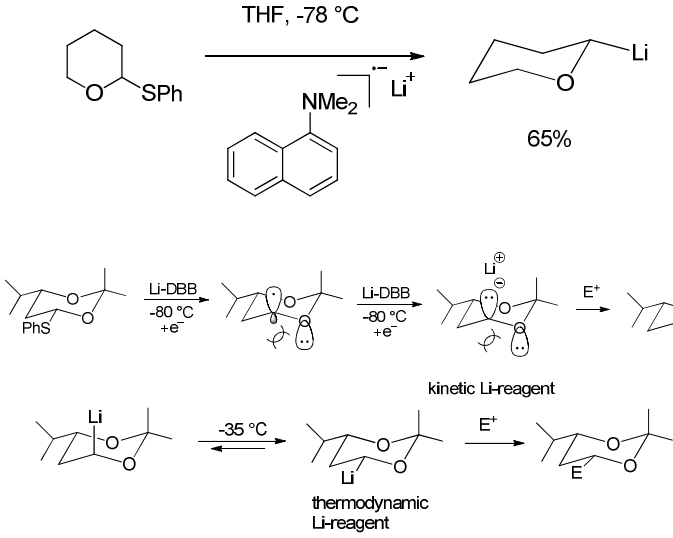
T. Blümke, Y.-H. Chen, P. Knochel *Nature Chemistry*, **2010**, *2*, 313



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

28

Extension to insertion reactions to C-S bonds



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

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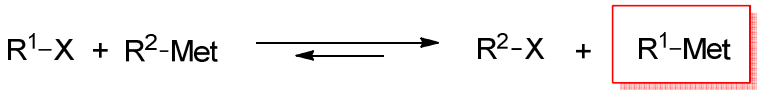
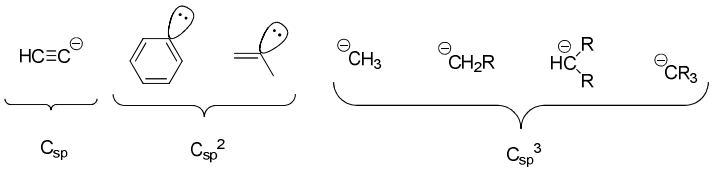
The Halogen-Metal-Exchange



driving force: the most stable carbanion is always formed



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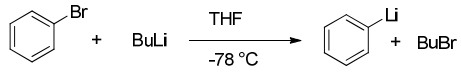
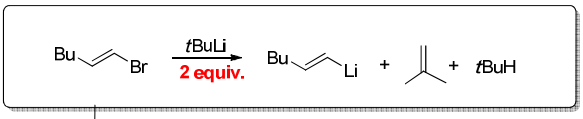
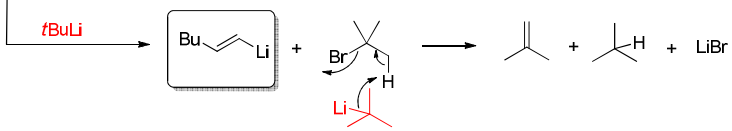
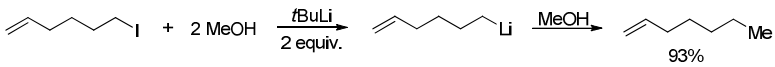
The Halogen-Metal-Exchange

1939: the Wittig-Gilman reaction









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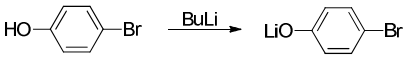
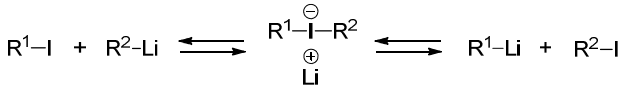
The Halogen-Metal-Exchange

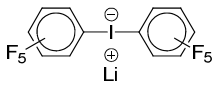


I >> Br >> Cl

rate of the halogen/metal exchange

mechanism:



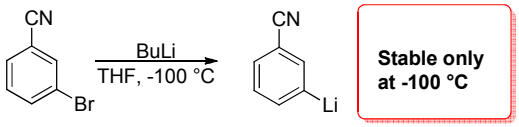


has been isolated

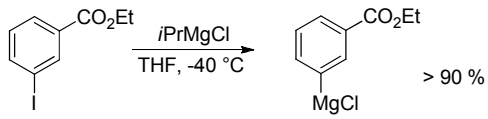
H. J. Reich, A. W. Sanders, A. T. Fiedler, M. J. Bevan *J. Am. Chem. Soc.* **2002**, *124*, 13386

32

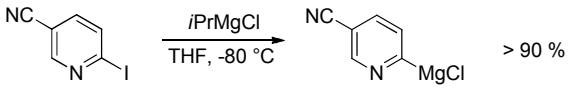
The Halogen-Metal-Exchange : tolerance of functional groups



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



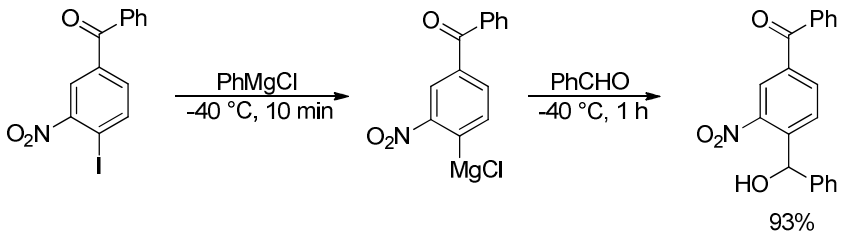
M. Rottländer, P. Knochel, Angew. Chem. Int. Ed. 1998, 40, 1801



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

33

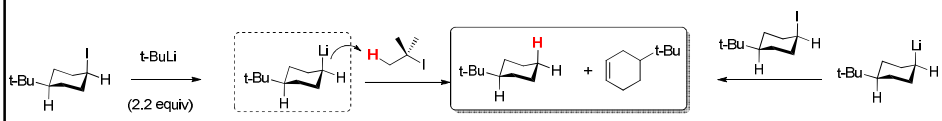
The iodine- magnesium-exchange: compatibility with a nitro group



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

34

A secondary iodine/lithium exchange on cyclohexyl iodides

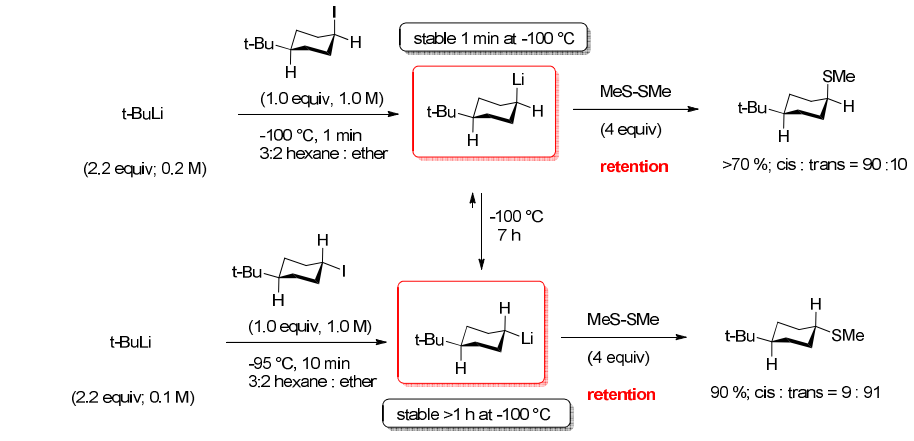


see W.F. Bailey, J.D. Brubaker, K.P. Jordan, *J. Organomet. Chem.* **2003**, *681*, 210

Stephanie SEEL

35

A secondary iodine/lithium exchange on cyclohexyl iodides



Stephanie SEEL

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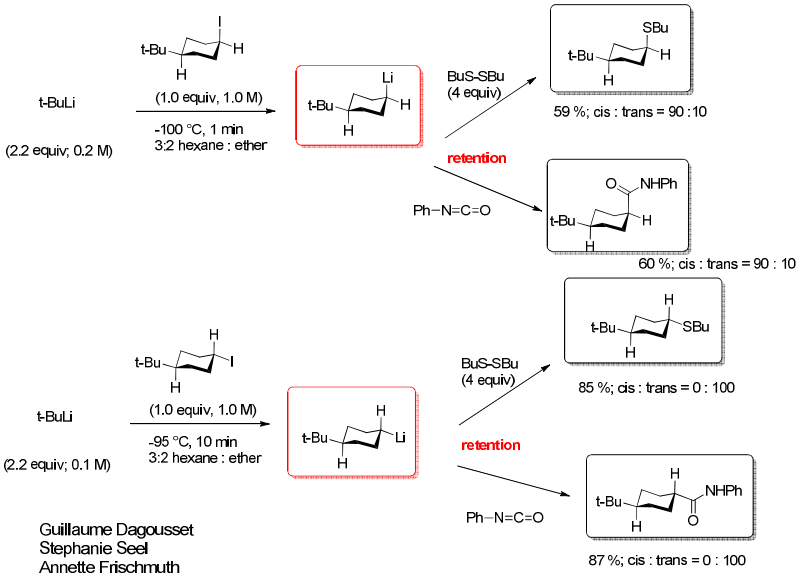
A secondary iodine/lithium exchange on cyclohexyl iodides



Guillaume Dagousset
Stephanie Seel
Annette Frischmuth

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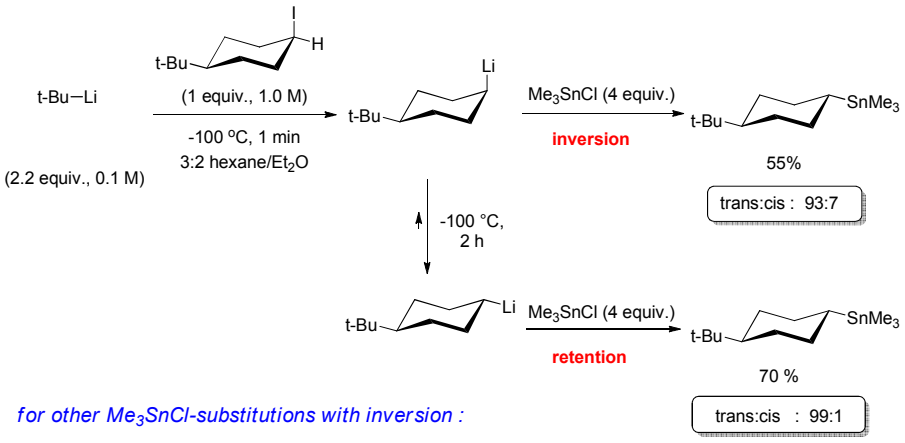
Quenching with Me3SnCl with inversion



for other Me_3SnCl-substitutions with inversion :

D. Hoppe *Angew.Chem.Int.Ed.Engl.* **1990**, *29*, 1424; *Chem. Eur. J.* **2001**, *7*, 423
J. Clayden *Tetrahedron Lett.* **1992**, *38*, 2568;
P. Beak, *J. Am. Chem. Soc.* **1997**, *119*, 11561;
R. E. Gawley, *J. Am. Chem. Soc.* **2000**, *122*, 3344.

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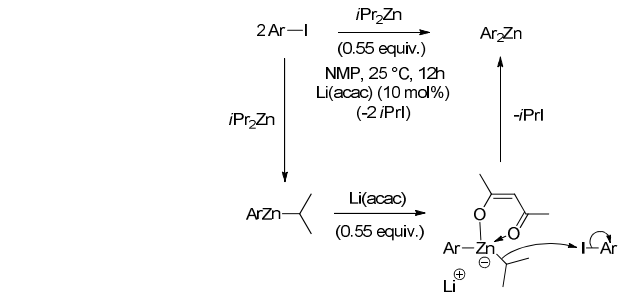
Guillaume DAGOUSSET

The iodine/zinc-exchange

catalysis of the halogen-metal exchange



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

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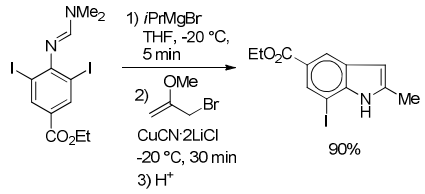
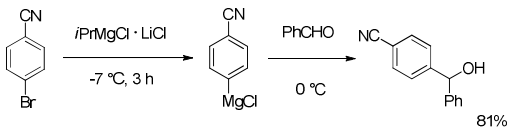
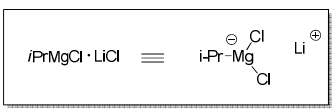
The Halogen-Metal-Exchange

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

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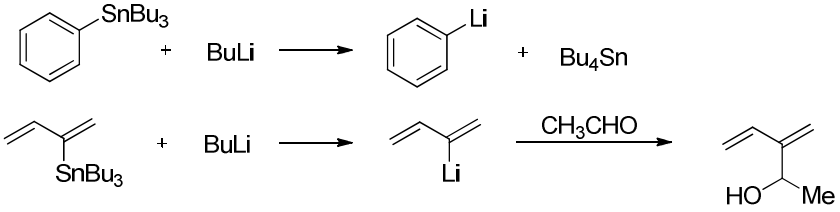
Transmetalation

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

the most stable carbanion is linked to the most electropositive metal



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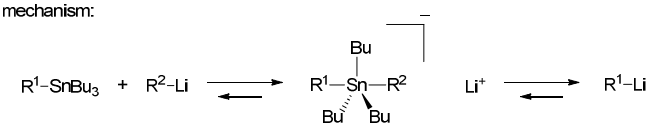
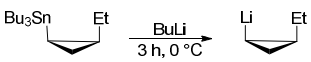
Transmetalation

mechanism:



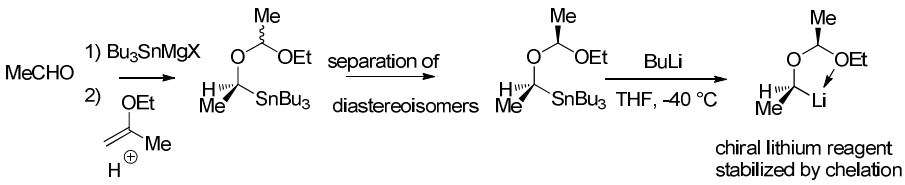
the most stable Li-organometallic is formed



configurational stable

Li-reagent due to the ring strain

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



chiral lithium reagent
stabilized by chelation

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

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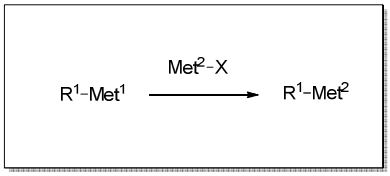
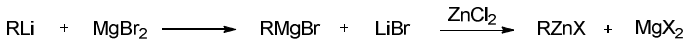
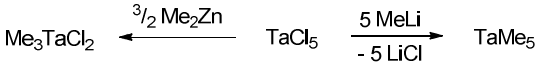
Transmetalation

b)







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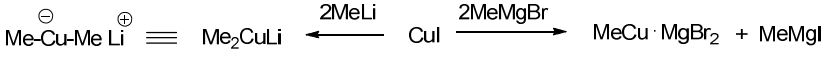
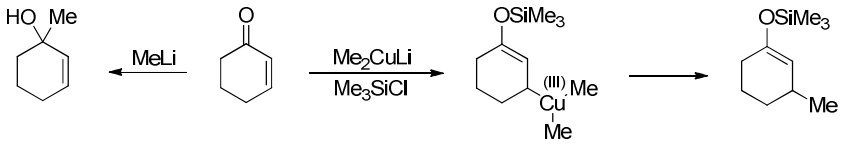
Transmetalation





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

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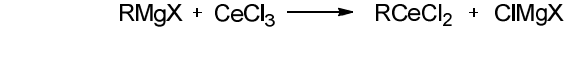
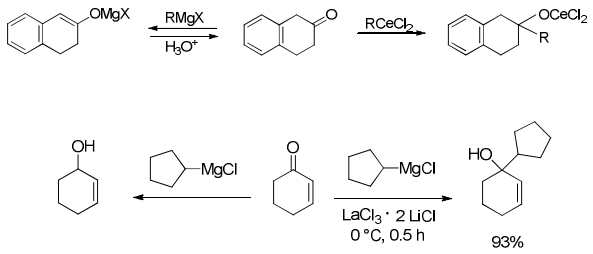
Transmetalation



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



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

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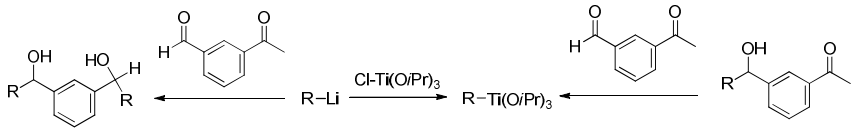
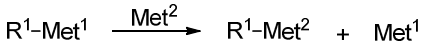
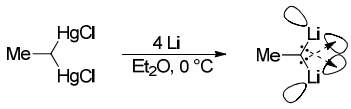
Transmetalation



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





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

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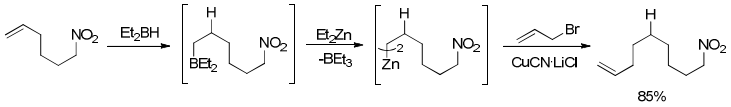
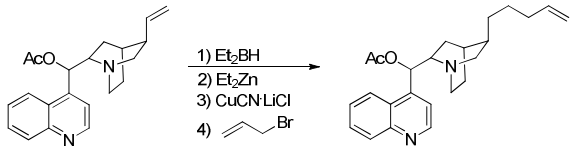
Transmetalation

boron / zinc-exchange



85%



95%

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

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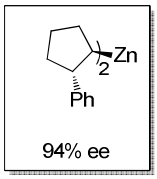
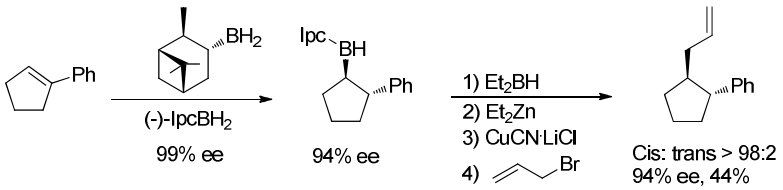
Transmetalation

boron / zinc-exchange



94% ee



99% ee

94% ee

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

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

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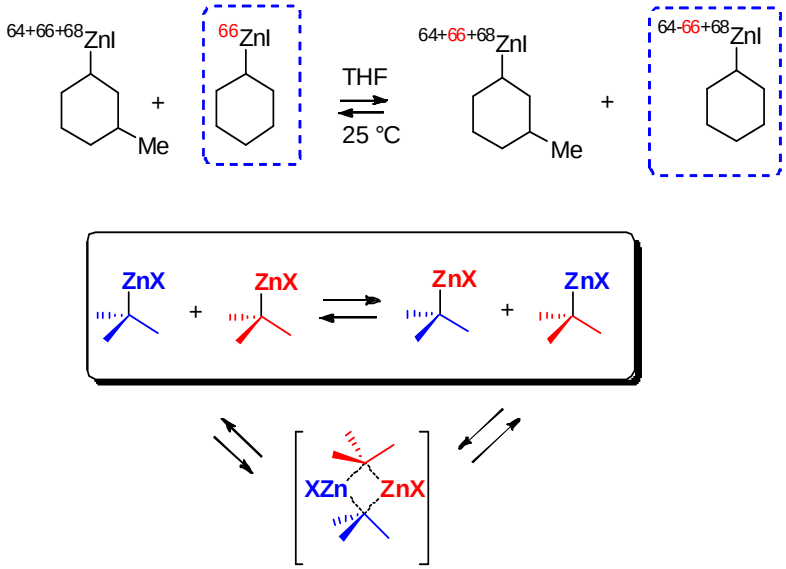
Nature of the carbon-zinc bond



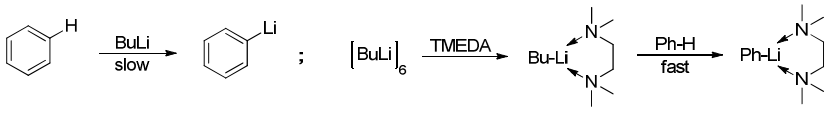
Metalation (starting from a compound with an acid proton)

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

$R^{2\ominus}$ must be more stable than $R^{1\ominus}$ $\Longrightarrow$ pKa(R1-H) > pKa(R2-H) (thermodynamic criteria)

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

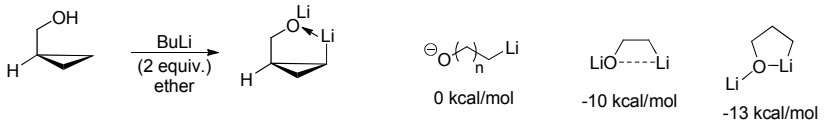
kinetic criteria (kinetic acidity)



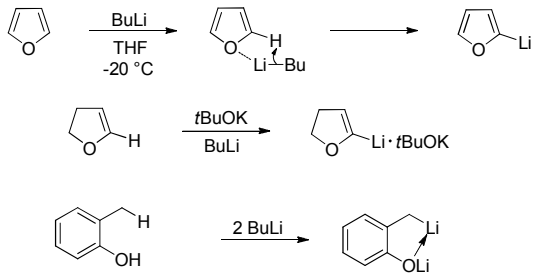
$PhCH_2Li$ reacts with benzene 10^4 times faster than with MeLi

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

Directed metalation

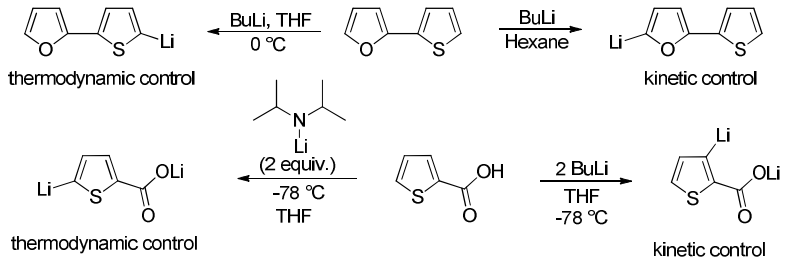


Directed metalation

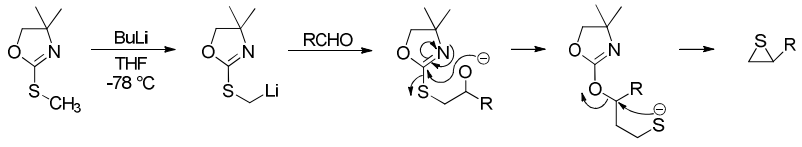


51

Metalation



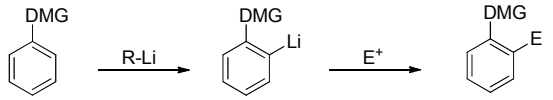
rearrangement



52

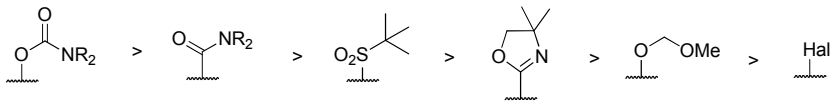
Metalation

directed lithiation



DMG = directing metalating group

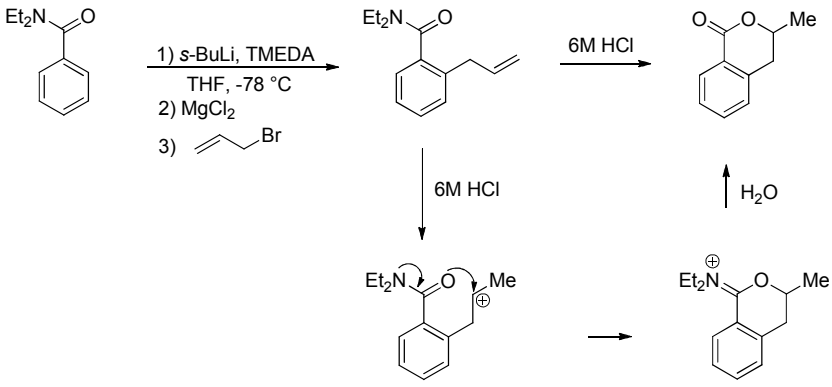
V. Snieckus, *Chem Rev*. **1990**, *90*, 879



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

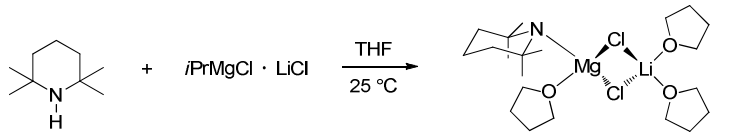
53

Metalation



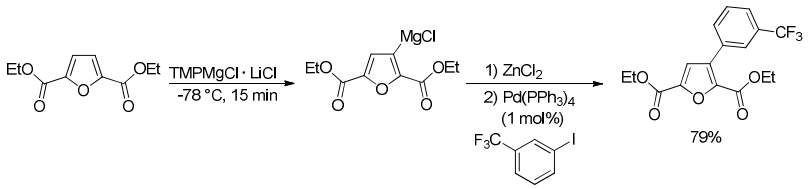
54

Metalation



TMPMgCl·LiCl (1.2 M in THF)

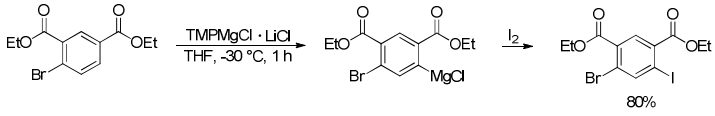
A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2006**, *45*, 2958
R. E. Mulvey, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079



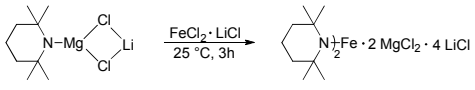
F. M. Piller, P. Knochel *Org. Lett*. **2009**, *11*, 445

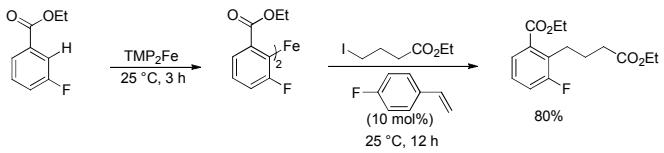
55

Metalation



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

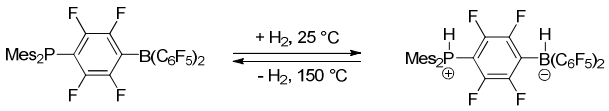




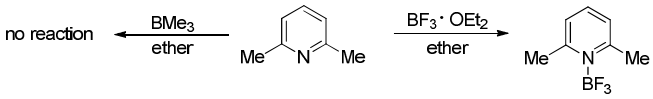
S. Wunderlich, P. Knochel *Angew. Chem. Int. Ed.* **2009**, *48*, 9717

56

Frustrated Lewis Pairs



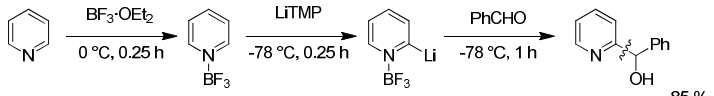
D. Stefan, G. Erker *Angew. Chem. Int. Ed.* **2010**, *49*, 46



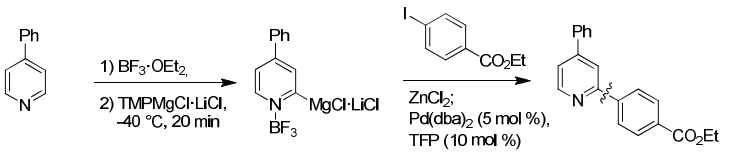
H. C. Brown *J. Am. Chem. Soc.* **1942**, *64*, 325

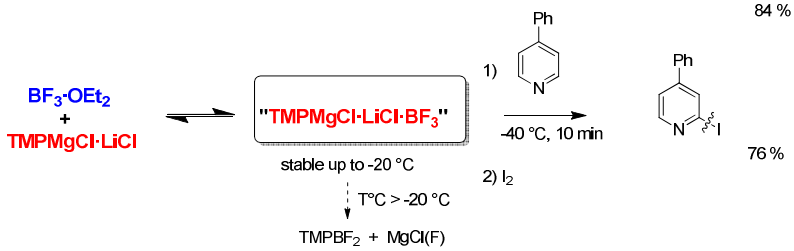
57

Frustrated Lewis Pairs



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



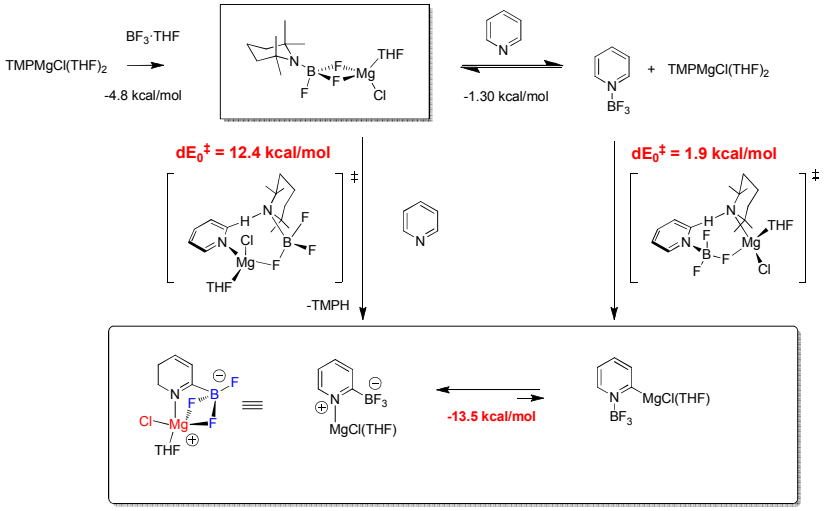


M. Jaric, B. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel *Angew. Chem. Int. Ed.* **2010**, *49*, 5451

58

Frustrated Lewis Pairs

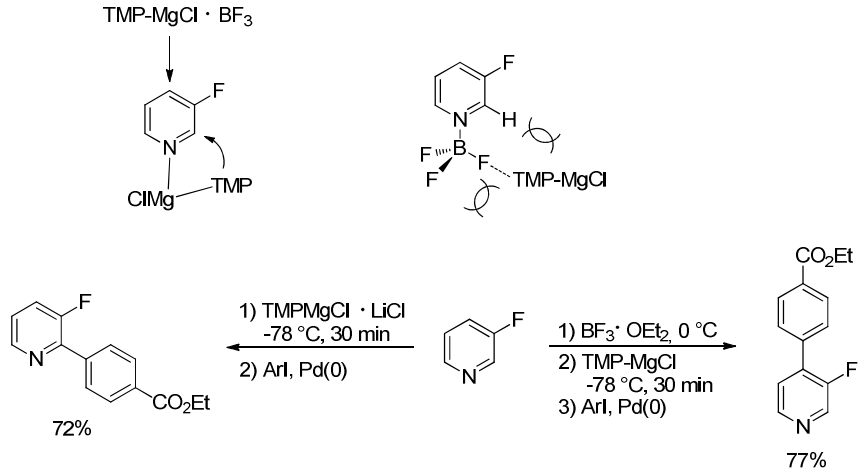
B3LYP/6-31G,def2-SVP**



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

59

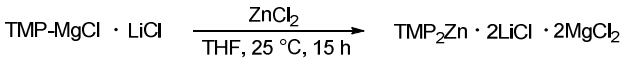
Frustrated Lewis Pairs



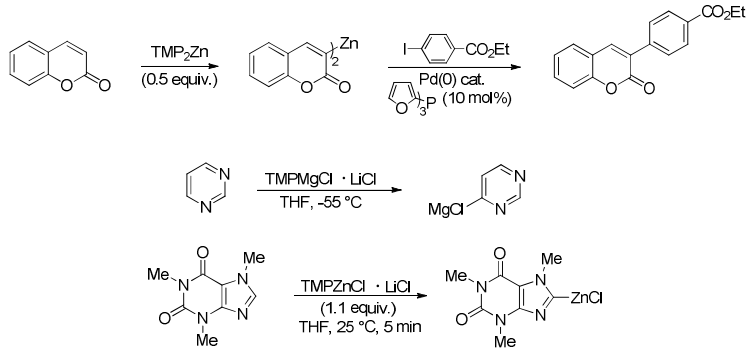
Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.

60

Metalation



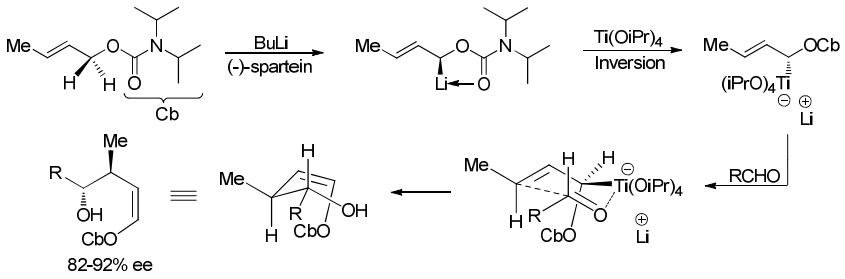
S. Wunderlich, P. Knochel *Angew. Chem. Int. Ed*. **2007**, *46*, 7685



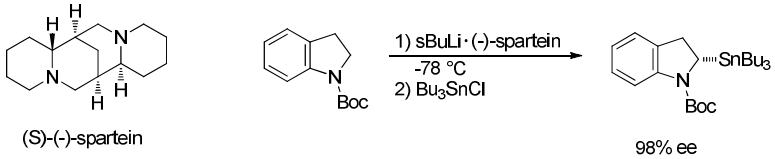
M. Mosrin, P. Knochel *Org. Lett*. **2008**, *10*, 2497
M. Mosrin, P. Knochel *Chem. Eur. J.* **2009**, *15*, 1468
M. Mosrin, P. Knochel *Org. Lett*. **2009**, *11*, 1837

61

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



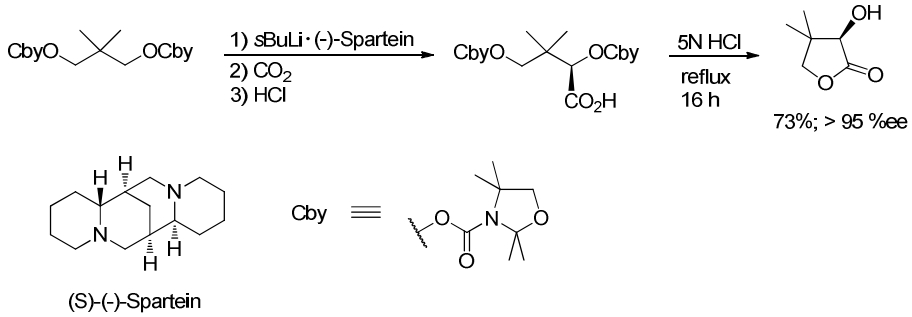
D. Hoppe, et al. *Pure Appl. Chem*. **1994**, *66*, 1479.



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

62

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

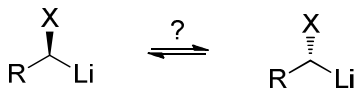


(S)-(-)-Spartein

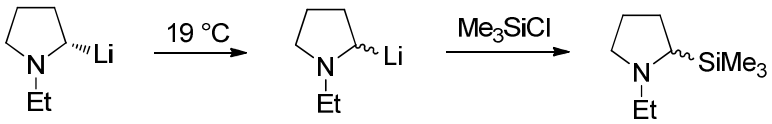
D. Hoppe *Tetrahedron Lett*. **1992**, *33*, 5327

63

Configurational stability



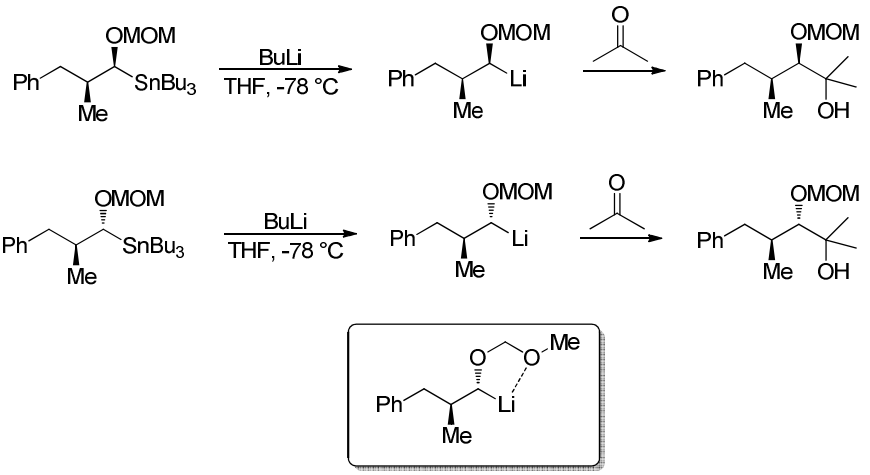
X=Br, SePh, SPh, OCH_2OMe, $OCONiPr_2$



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

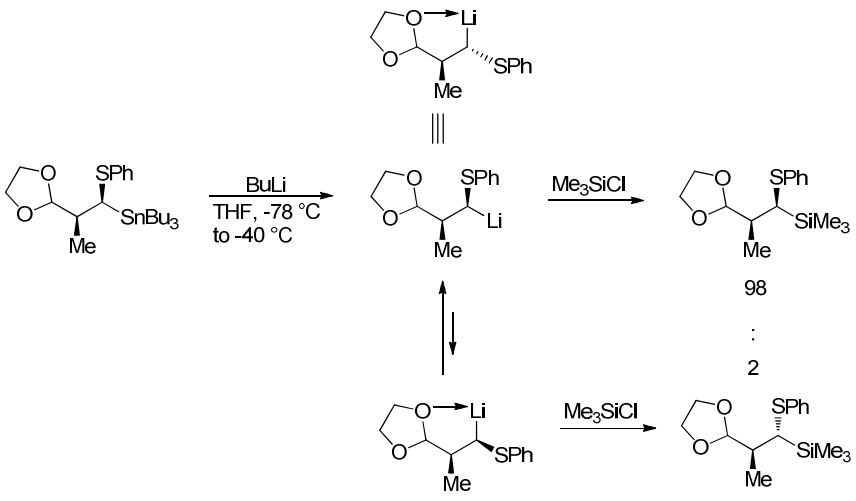
64

Diastereoselective transmetalation



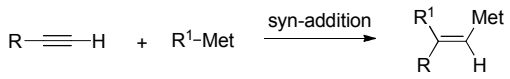
W. C. Still J. *Am. Chem. Soc*. **1980**, *102*, 1201

Diastereoselective transmetalation

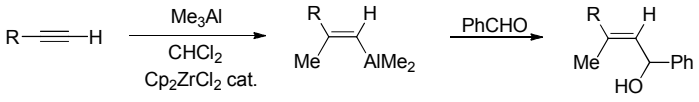


P. G. McDougal, *Tetrahedron Lett*. **1988**, *29*, 2547

Carbometalation

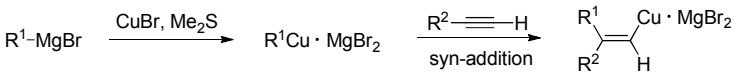


Negishi-reaction: carboalumination



79%

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

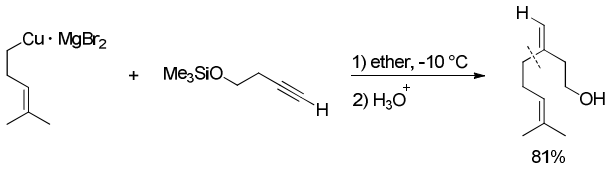


> 90%

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

67

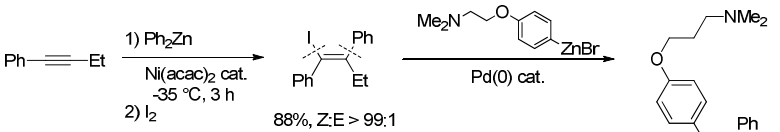
Carbometalation



81%

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

Tamoxifen-Synthesis: Carbozincation



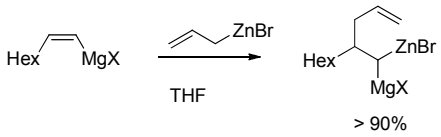
88%, Z:E > 99:1

75%, Z:E > 99:1

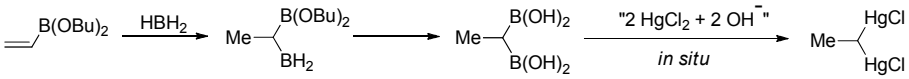
T. Stüdemann, P. Knochel *Angew. Chem.* **1997**, *109*, 132

68

Carbometalation, hydrometalation



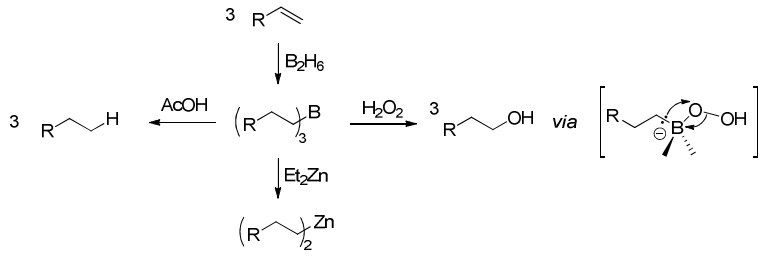
P. Knochel, J. F. Normant *Tetrahedron Lett*. **1986**, *27*, 1039; 1043; 4427

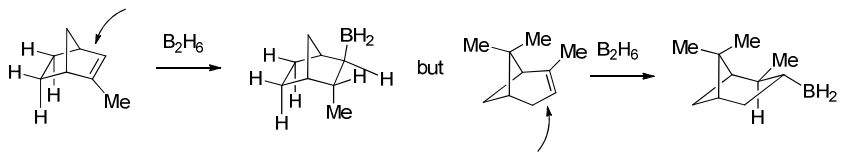


D. Matteson, *J. Org. Chem*. **1964**, *29*, 2742

Hydrometalation and application of organoboranes in organic chemistry

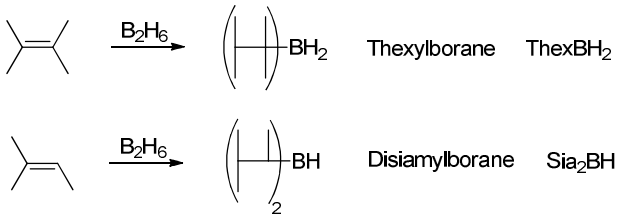
hydroboration





Hydroboration

selective hydroborating reagents

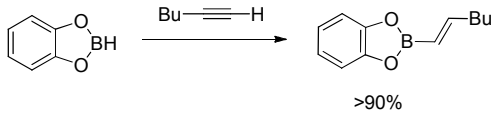


H. C. Brown, E. Negishi *J. Am. Chem. Soc*. **1975**, *97*, 2799

71

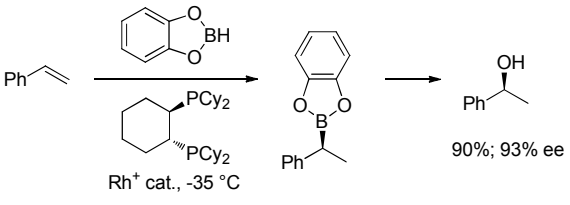
Hydroboration

catecholborane



>90%

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



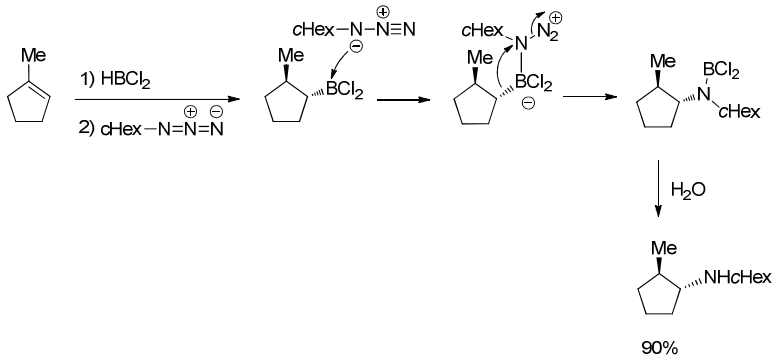
90%; 93% ee

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

72

Hydroboration

amination



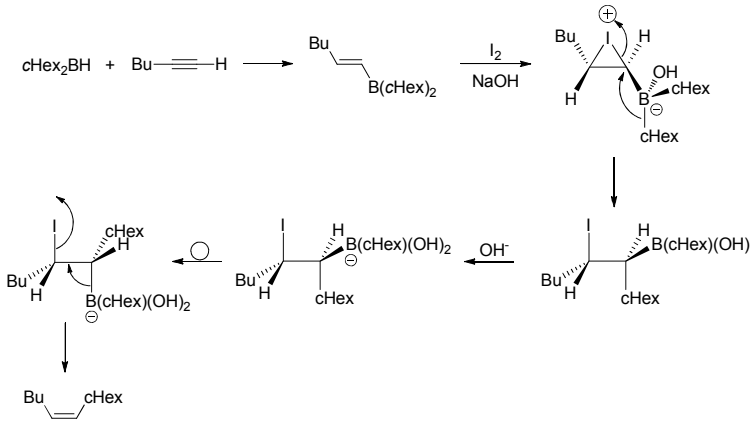
H. C. Brown, et al. *Tetrahedron* **1987**, *43*, 4079

73

Hydroboration

stereoselective synthesis of olefins

Z-olefins



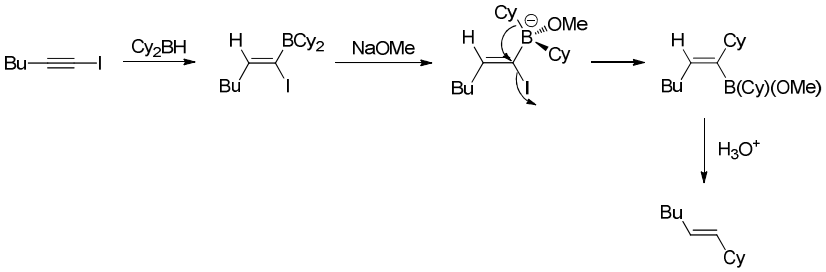
G. Zweifel, et al. *J. Am. Chem. Soc*. **1972**, *94*, 6560.

74

Hydroboration

stereoselective synthesis of olefins

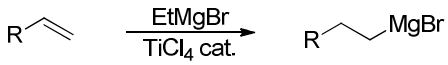
E-olefins

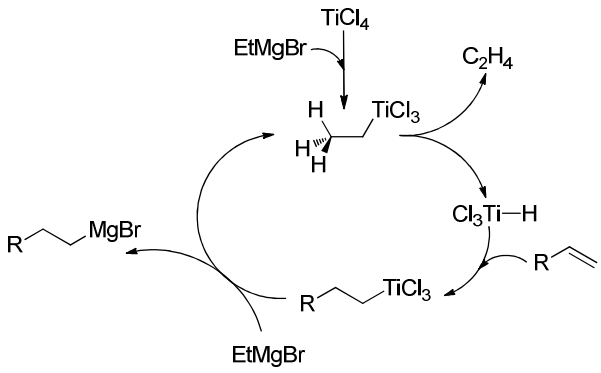


H. C. Brown, et al *J. Org. Chem.* **1989**, *54*, 6064.

75

Hydromagnesiation

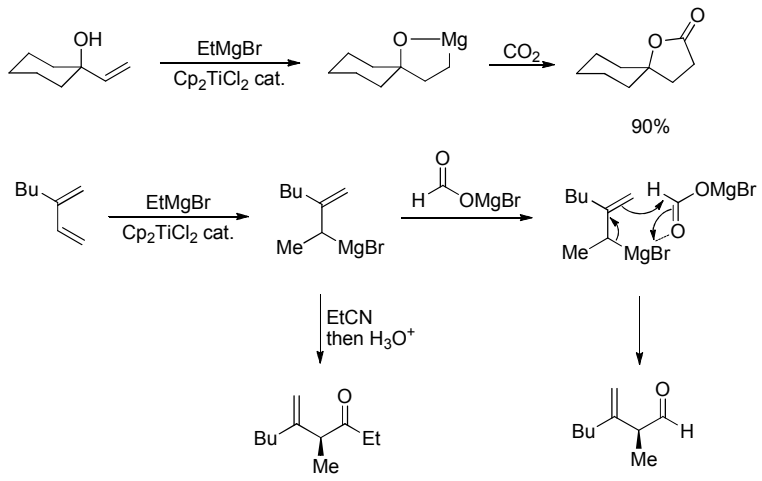




F. Sato, *Chem. Rev*. **2000**, *100*, 2835; *Synlett* **2000**, 753

76

Hydromagnesiation



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

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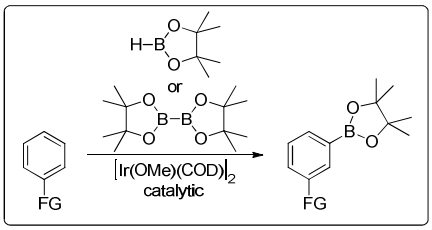
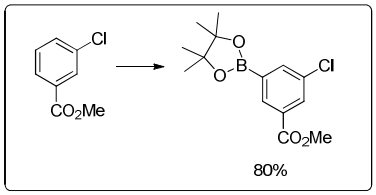
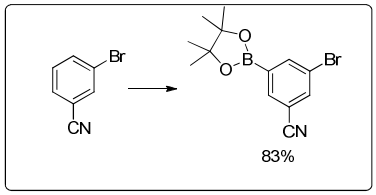
Synthesis of aryl boronic acids

transition-metal catalyzed synthesis of aryl boronic acids



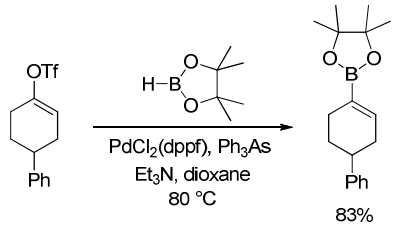




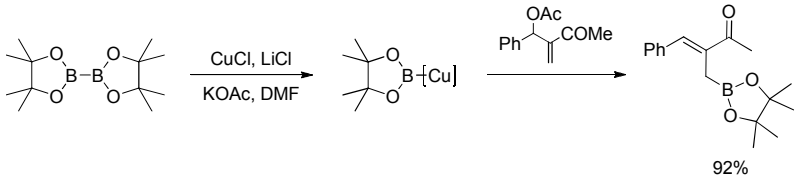
J. F. Hartwig, N. Miyaura, *Chem. Comm*. **2003**, 2924;
J. Am. Chem. Soc. **2002**, *124*, 390; *Angew. Chem. Int. Ed*. **2002**, *45*, 3056

78

Synthesis of aryl boronic acids



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

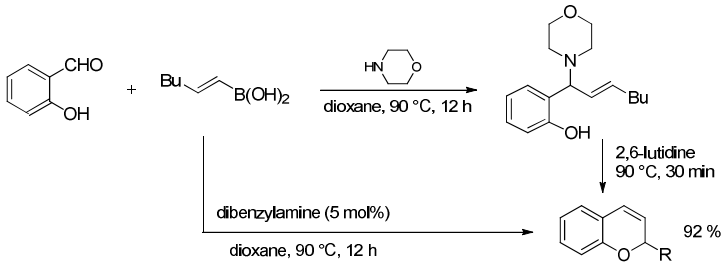


P. V. Ramachandran *Org. Lett*. **2004**, *6*, 481

79

Reactivity of unsaturated boronic derivatives

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



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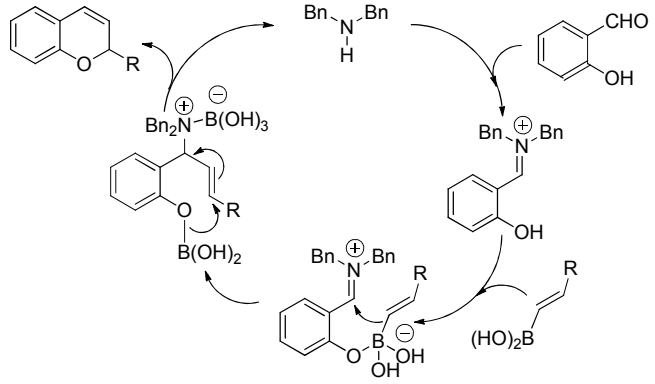
Reactivity of unsaturated boronic derivatives

The Petasis-reaction

mechanism



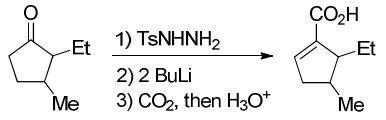
M. G. Finn, *Org. Lett*. **2000**, *2*, 4063

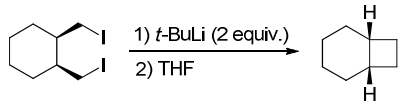
ÜBUNG

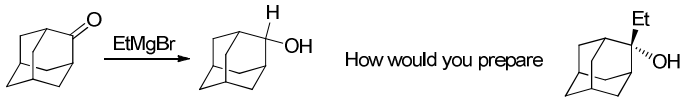
1. Problem set

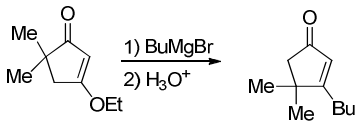
First Problem Set for OC IV

1) Give a mechanism for the following reactions:

a) 

b) 

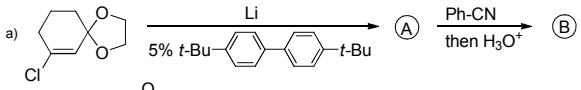
c) 

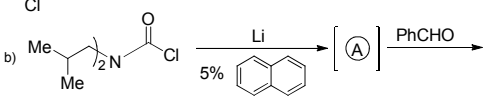
d) 

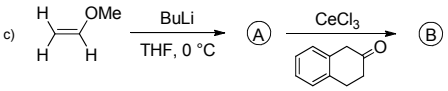
83

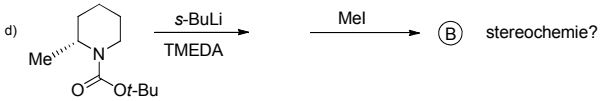
First Problem Set for OC IV

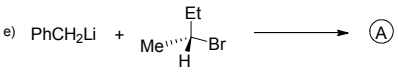
2) Give the following reaction products:

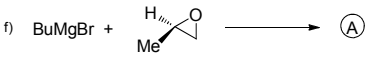
a) 

b) 

c) 

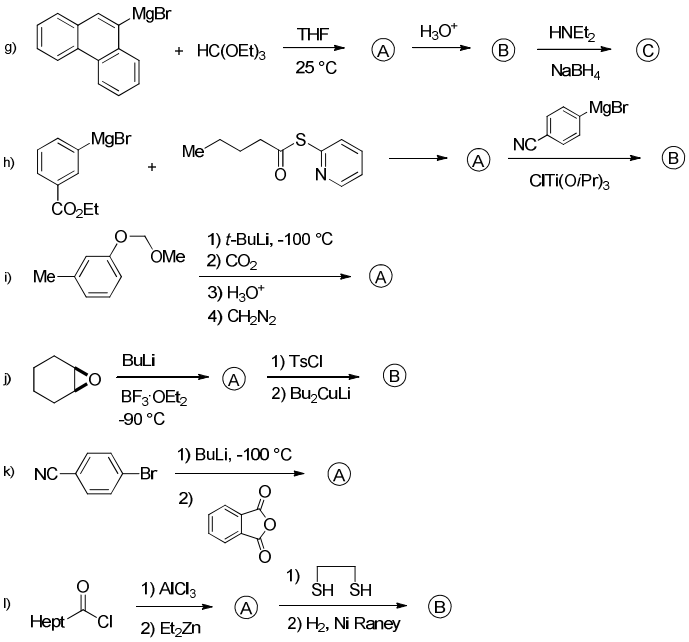
d) 

e) 

f) 

84

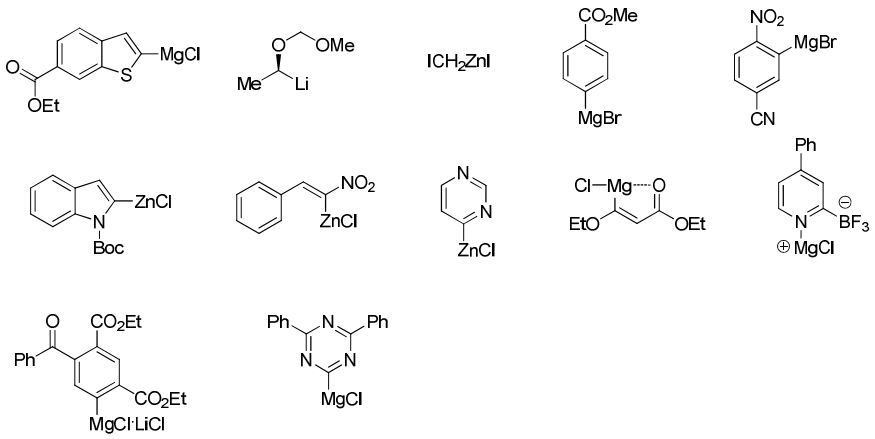
First Problem Set for OC IV



85

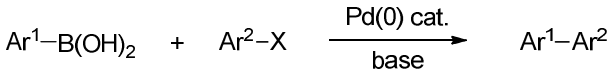
First Problem Set for OC IV

3. How you would prepare following organometallics:



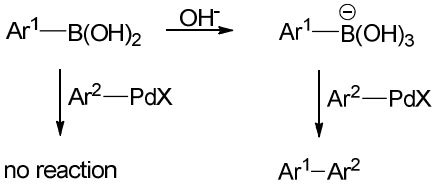
86

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**

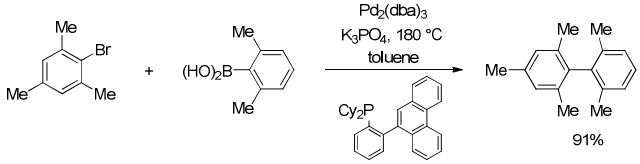
Key step



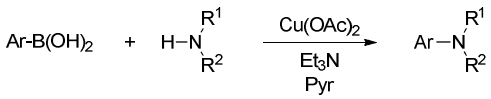
S. Buchwald, *J. Am. Chem. Soc*. **2002**, *124*, 1162
C. Amatore, A. Jutand, G. Le Duc *Chem. Eur. J*. **2011**, *17*, 2492
B. P. Carrow, J. F. Hartwig *J. Am. Chem. Soc*. **2011**, *133*, 2116

87

The Suzuki cross-coupling reaction



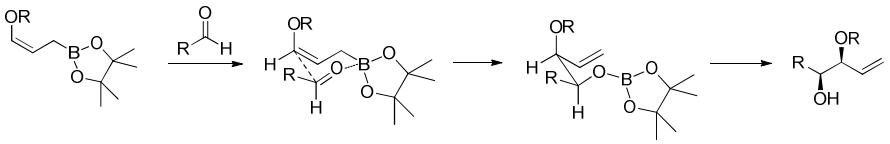
R. E. Sammelson, M. J. Kurth *Chem. Rev*. **2001**, *101*, 137



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

88

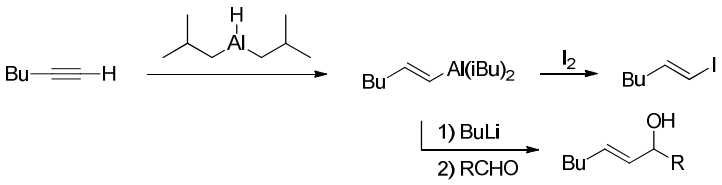
Chemistry of allyl boranes



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

89

Hydroalumination

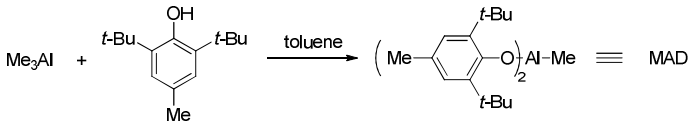


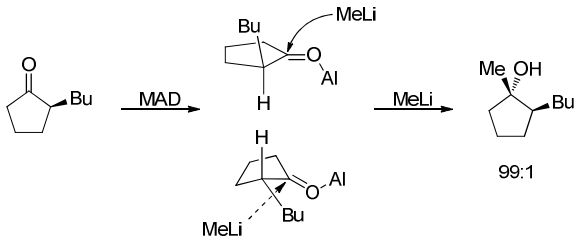
G. Zweifel, *Org. React*. **1984**, *32*, 375

90

Hydroalumination

Special Al-reagents

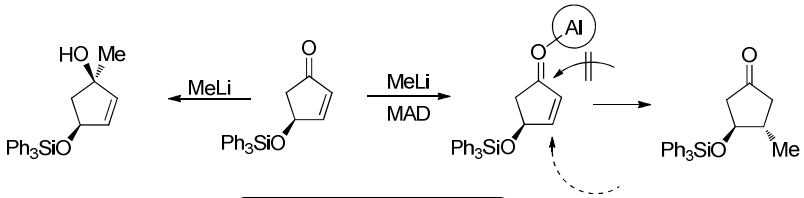


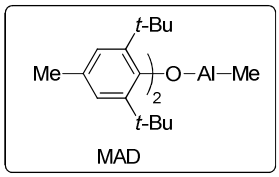


H. Yamamoto *J. Am. Chem. Soc*. **1988**, *110*, 3588
H. Yamamoto *Chem. Comm*. **1997**, 1585

91

Hydroalumination



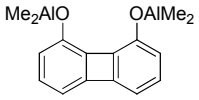


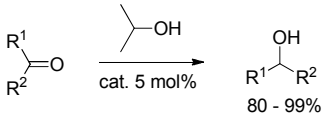
K. Maruoka, H. Yamamoto, Kagaku, Zokan (Kyoto, Japan) **1988**, *115*, 127
S. Nagahara, K. Maruoka, H. Yamamoto, *Bull Chem Soc*. **1993**, *66*, 3783

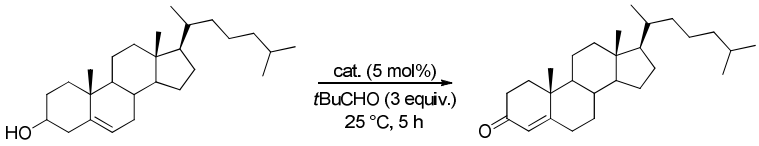
92

Hydroalumination

Verley-Meerwein-Ponndorf reduction

activating a carbonyl group twice  is possible using 

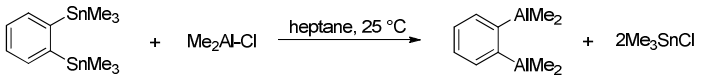




K. Maruoka *Angew. Chem.* **1998**, *110*, 2524

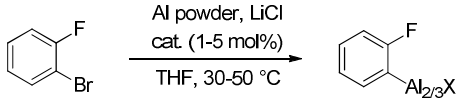
93

Other preparation of aluminium compounds



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

Direct synthesis of organoaluminium reagents



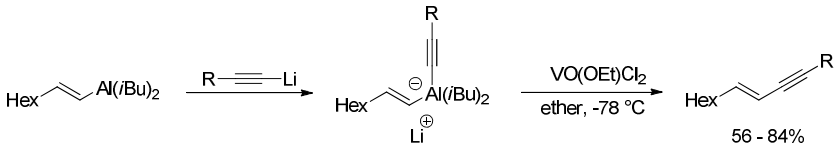
cat. = $InCl_3$, $BiCl_3$, $PbCl_2$, $TiCl_4$

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

94

Hydroalumination

Reactivity



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

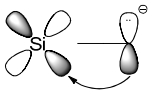
95

The organic chemistry of main-group organometallics

Silicium

The effect of a Me_3Si-substituent:

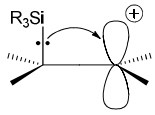
1) inductive effect: weak donor-effect
2) retrodonation of π-electrons (d-p bond)



empty d-orbital — filled p-orbital

stabilization of carbanions in α-position

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



stabilization of a cation in β-position

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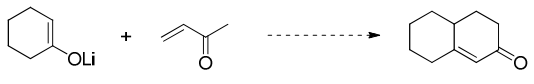
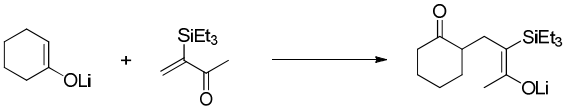
Silicium

Applications:



low yields



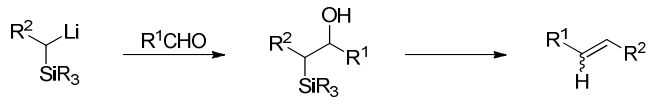
high yield: stabilized lithium enolate
(no polymerization)

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

97

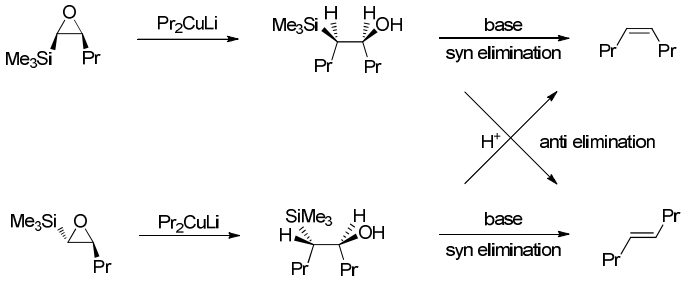
Silicium

Peterson olefination



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

Stereochemistry of the *Peterson*-elimination



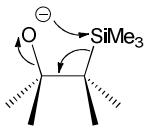
P. F. Hudrlik, D. Peterson, R. J. Rona *J. Org. Chem*. **1975**, *40*, 2263

98

Silicium

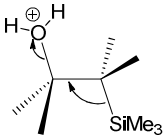
key steps:

basic media



syn elimination

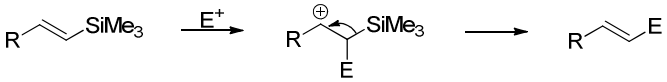
acidic media

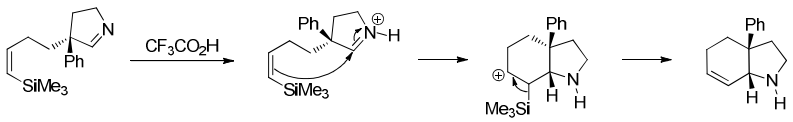


anti elimination

99

Reactivity of alkenylsilanes



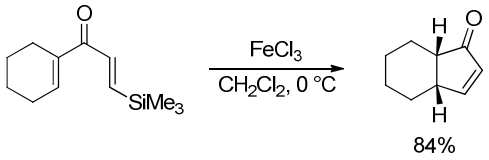


L. E. Overman, *Tetrahedron Lett*. **1984**, *25*, 5739

100

Reactivity of alkenylsilanes

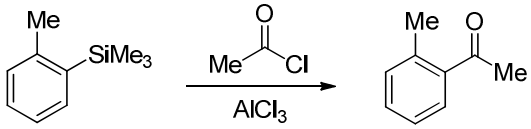
Sila-Nazarov-reaction



84%

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

Aromatic ipso-substitution

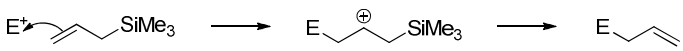


The reaction with $ArSnMe_3$ is 10^4 time faster

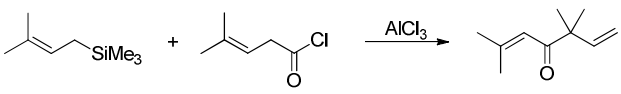
101

Allylic silanes in organic synthesis

General reactivity



Acylation



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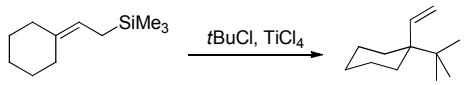
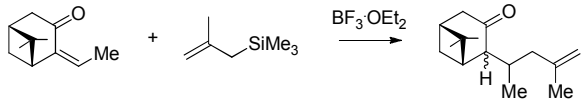
Allylic silanes in organic synthesis

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.

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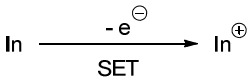
Indium

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



strong oxophilicity

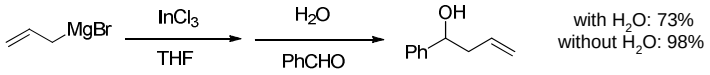
The first ionization potential of indium (5,8 eV)
is close to lithium and sodium

Key contributions:

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

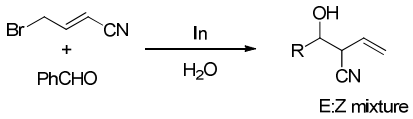
104

Indium. Allylation reactions



with H_2O: 73%
without H_2O: 98%

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



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

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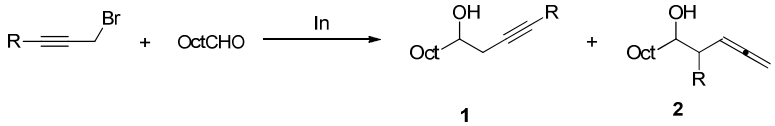
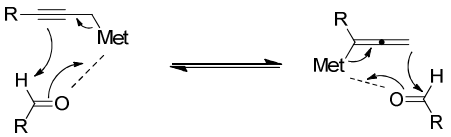
Indium



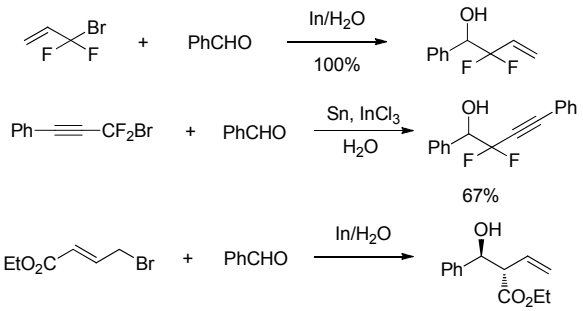


R	Conditions	Yield	Ratio **1** : **2**
Me_3Si	THF, InF_3 (10 mol%)	93	99:1
iPr_3Si	THF:H_2O (1:5)	52	5:95

T. P. Loh, *J. Am. Chem. Soc*. **2003**, *125*, 13042

106

Indium

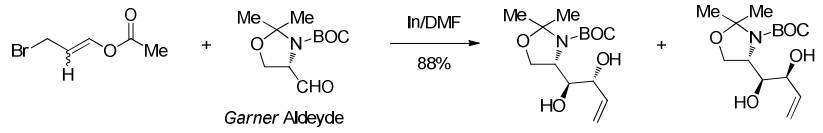


without $La(OTf)_3$: 59% anti:syn = 86 : 14
with $La(OTf)_3$: 99% anti:syn = 90 : 10

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

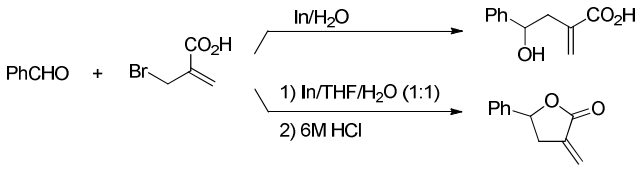
107

Indium



97 : 3

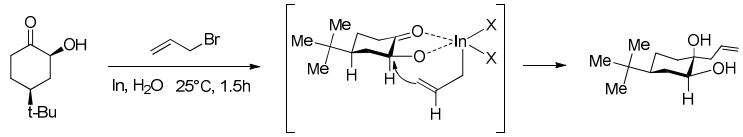
M. Lombardo, *Pure Appl. Chem*. **2004**, *76*, 657

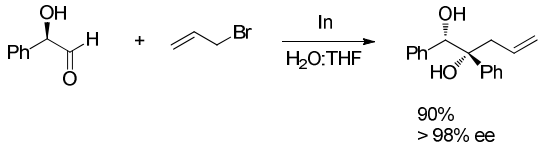


T. H. Chan, *J. Org. Chem*. **1995**, *60*, 4228

108

Indium



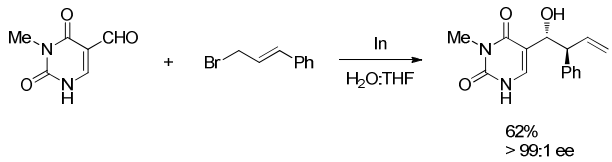


L. A. Paquette, *Org. Lett*. **2000**, *2*, 1263

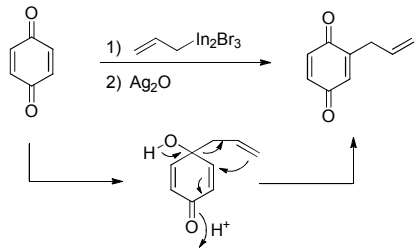
109

Indium

Applications in nucleoside chemistry:



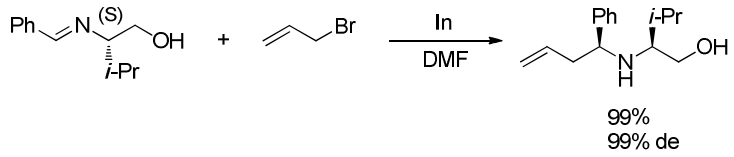
S. Kumar, *Tetrahedron Lett*. **2001**, *42*, 7039



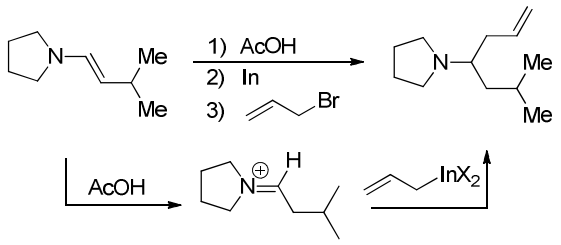
S. Akiva, *J. Organomet. Chem*. **1991**, *415*, 7

110

Indium



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

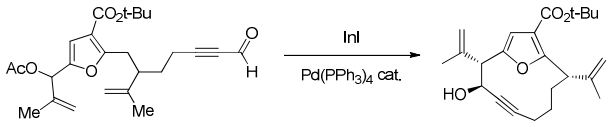


P. Mosset *Tetrahedron Lett*. **1995**, *36*, 6055
P. Mosset *Chem. Eur. J*. **1997**, *3*, 1064

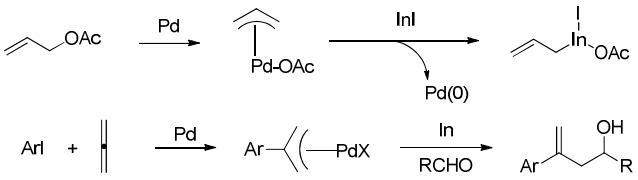
111

Indium

Applications in natural product syntheses:



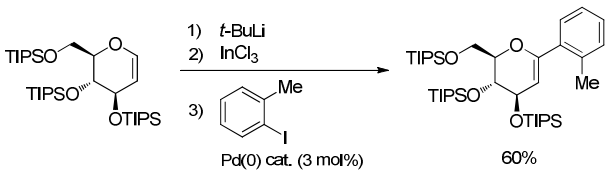
J. A. Marshall, *J. Org. Chem*. **1999**, *64*, 5193



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

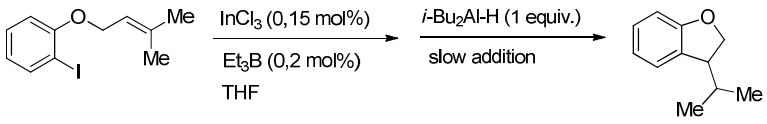
112

Indium



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

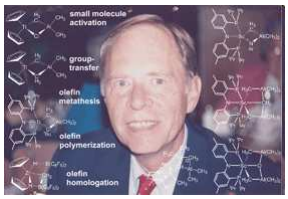
radical reaction

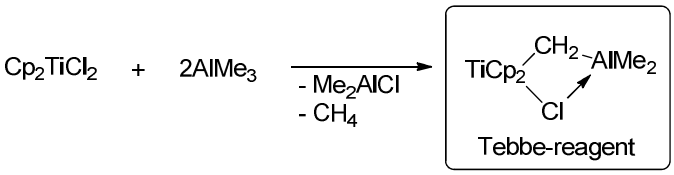


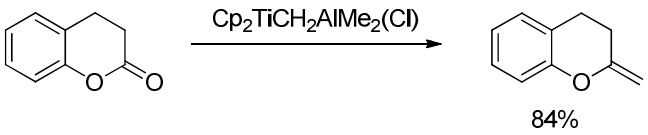
K. Oshima, *Tetrahedron*, **2003**, *59*, 6627

113

Early transition metal organometallics: Titanium





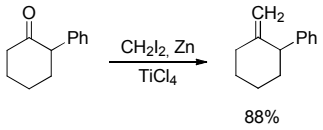


S. H. Pine *Org. React*. **1993**, *43*, 1

114

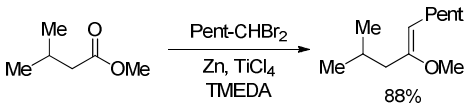
Titanium

Lombardo-reagent

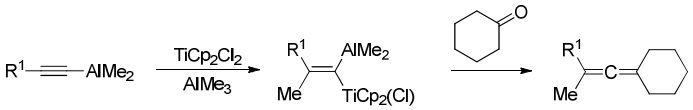


88%

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



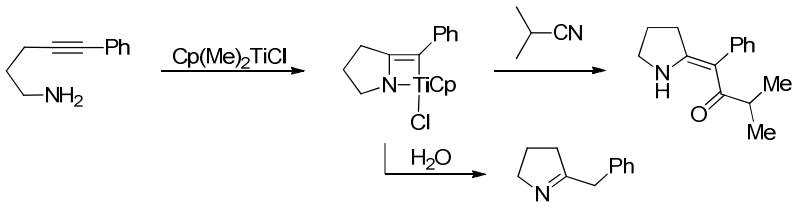
88%



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

115

Titanium

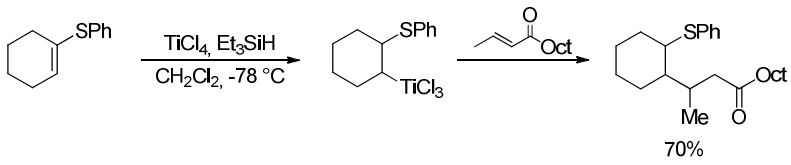


T. Livinghouse, *J. Am. Chem. Soc*. **1992**, *114*, 5459

116

Titanium

Hydrotitanation

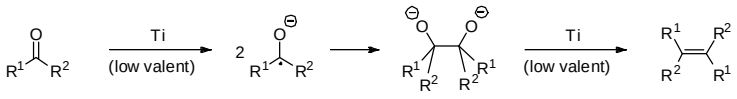


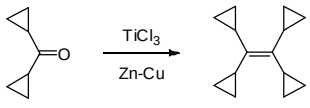
70%

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

Titanium

Reductive coupling: The McMurry Reaction

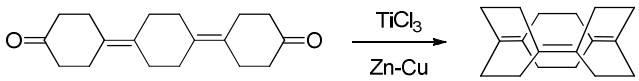


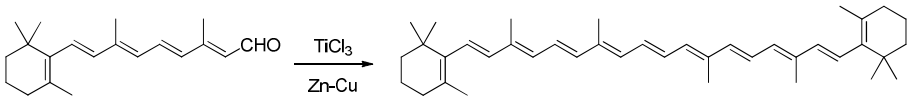


25%

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

Titanium





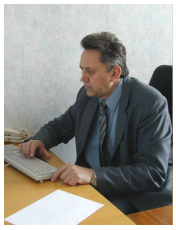
β-Caroten: 94%

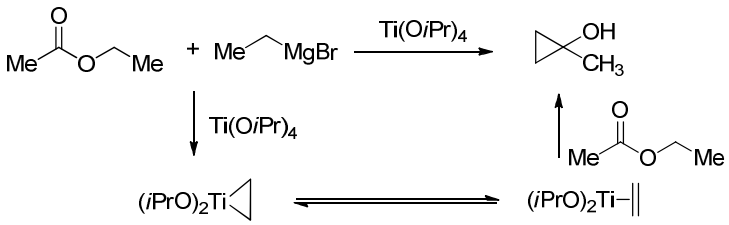
J. E. McMurry et al. *J. Am. Chem. Soc*. **1984**, *106*, 5018.

119

Titanium

Kulinkovich-reaction

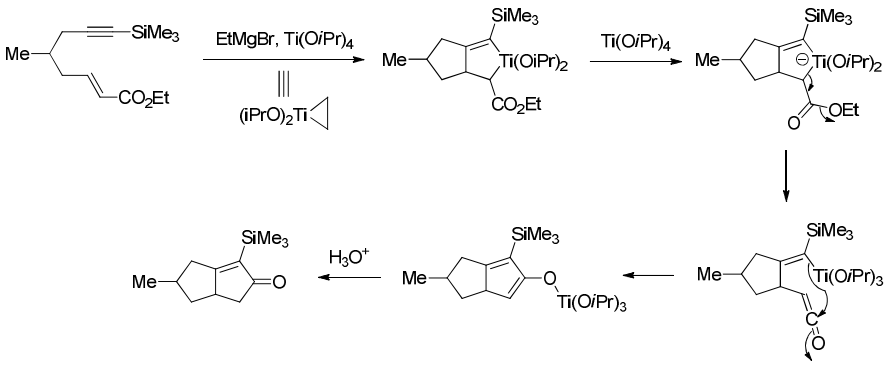




O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, T. S. Prityts kaya, *Zh. Org. Khim.* **1989**, 25, 2244.
O. Kulinkovich, S.V. Sviridov, D.A. Vasilevski, *Synthesis,* ***1991***, 234.

120

Titanium



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

121

Early transition metal organometallics: **Zirconium**

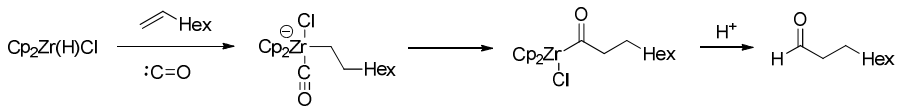
Schwartz's reagent:

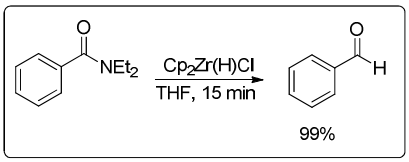
$$ZrCp_2Cl_2 \xrightarrow[THF]{LiAl(H)(OtBu)_3} Cp_2Zr(H)Cl \quad 90\%$$

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

122

Zirconium



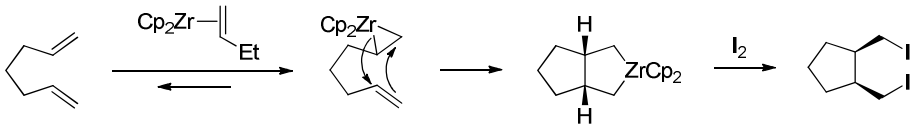


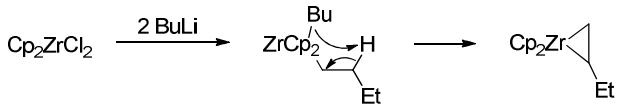
G. I. Georg *J. Am. Chem. Soc.* **2007**, *129*, 3408

123

Zirconium

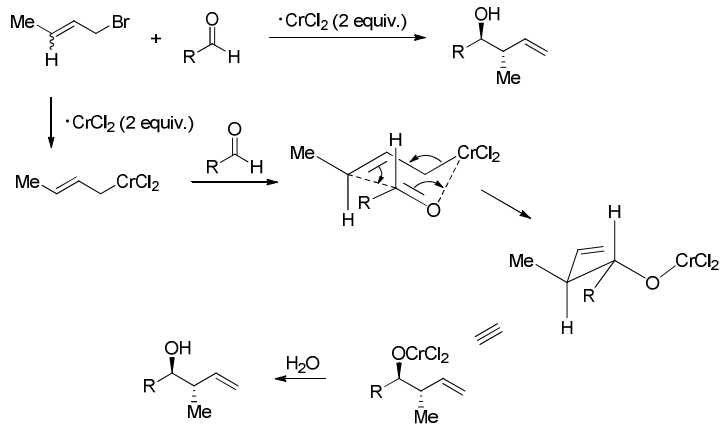
A Negishi reaction is involved:





124

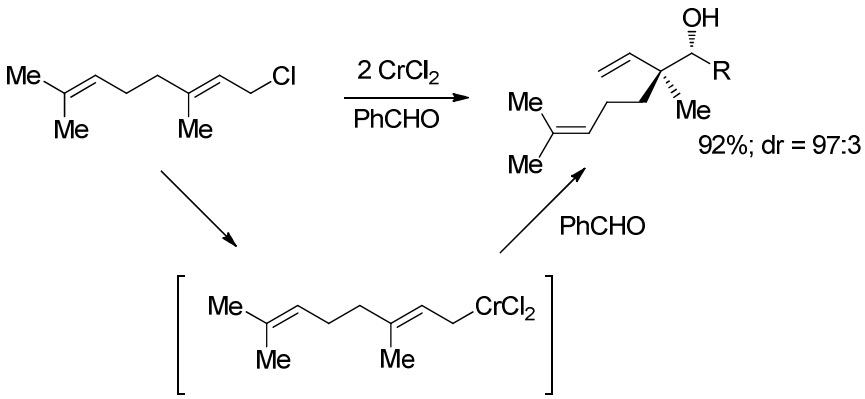
Early transition metal organometallics: Chromium



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

125

Chromium

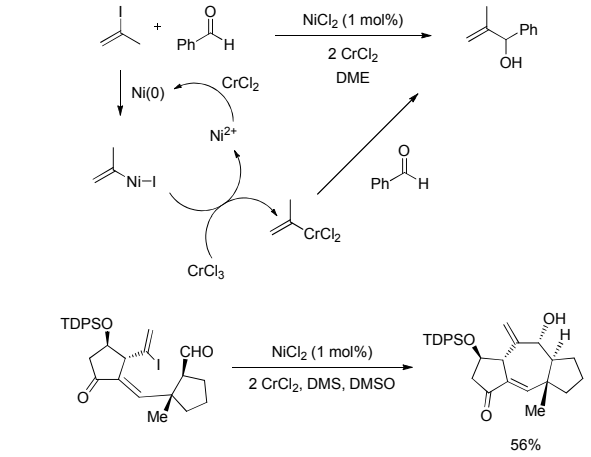


K. Belyk, M. J. Rozema, P. Knochel *J. Org. Chem*. **1992**, *57*, 4070.

126

Chromium

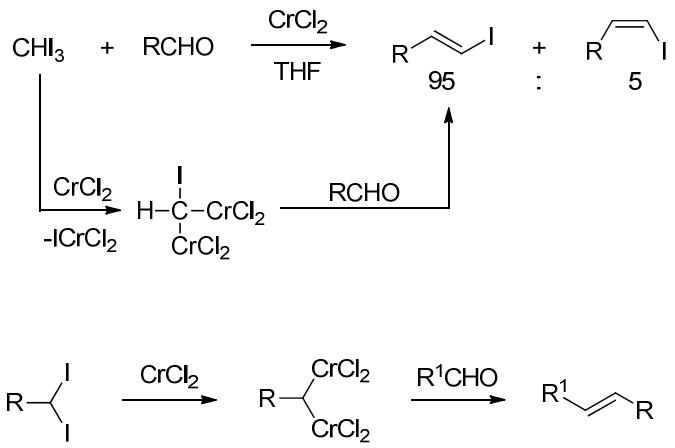
Hiyama-Kishi-reaction



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

127

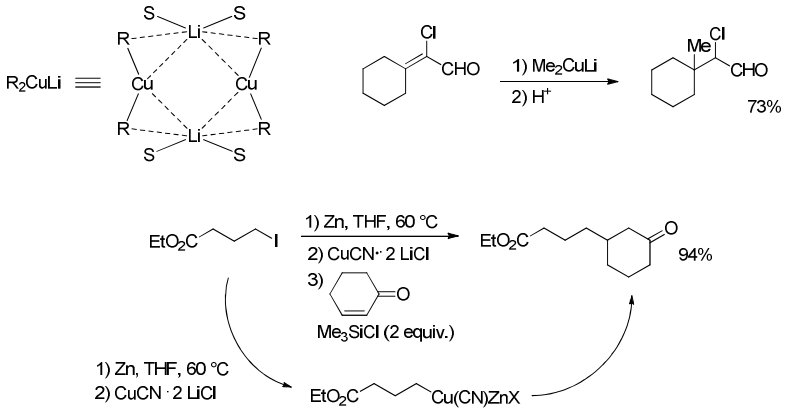
Chromium



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

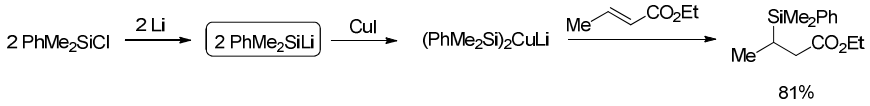
128

Early transition metal organometallics: Copper

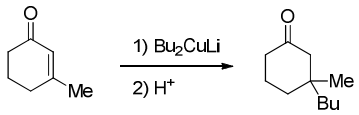


P. Knochel, et al. *J. Org. Chem.* **1988**, *53*, 2390.

Copper

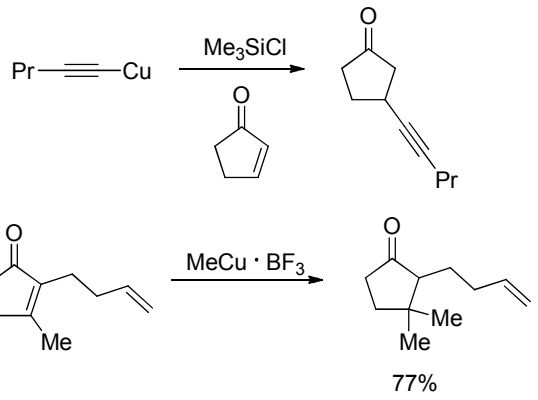


I. Fleming et al. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 1209.



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

Copper-mediated 1,4-addition

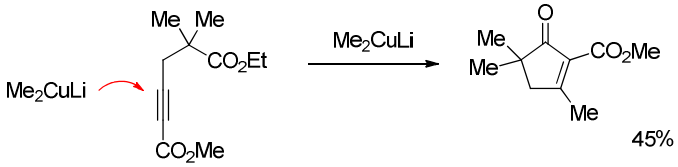


Y. Yamamoto, *Angew. Chem.* **1986**, *98*, 945.

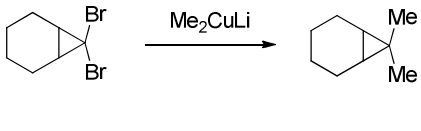
131

Copper-mediated reactions

Michael-addition



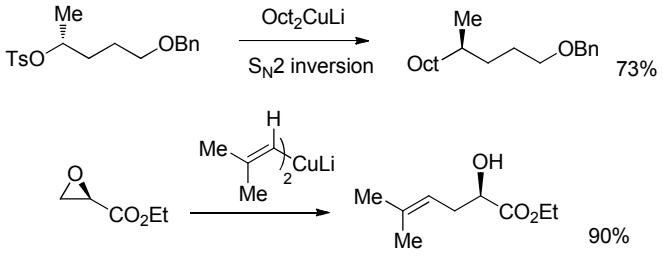
Substitution reactions

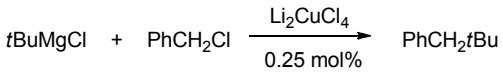


G. Posner, *Org. React.* **1975**, *22*, 253.
R. J. K. Taylor (Ed.), *Organocopper reagents*, Oxford University Press, Oxford, **1994**.

132

Copper; substitution reactions

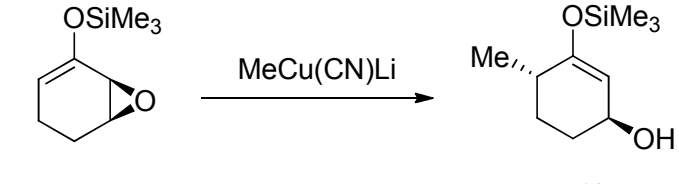


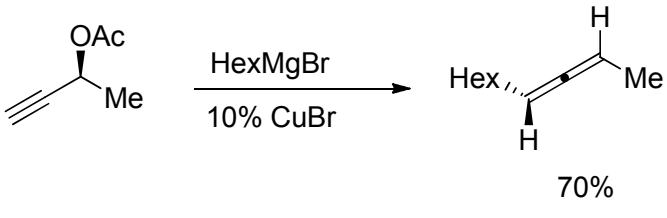


M. Larcheveque, Y. Petit, *Bull. Soc. Chim. Fr*. **1989**, *1*, 130.

133

Copper: allylic and propargylic substitution

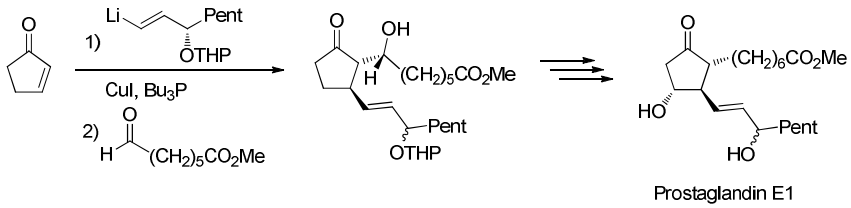




A. Alexakis, *Pure Appl. Chem*. **1992**, *64*, 387.

134

Copper: Prostaglandin synthesis



Prostaglandin E1

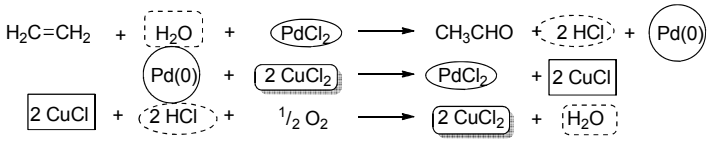
F. Sato *J. Org. Chem*. **1988**, *53*, 5590

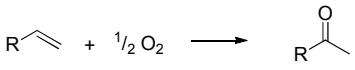
135

Palladium

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

Wacker-Reaction:

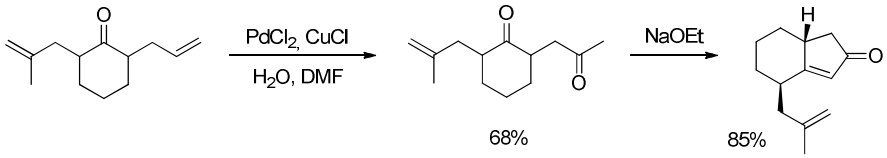




J. Schmidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, J. Sabel, *Angew. Chem. Int. Ed*. **1962**, *1*, 80.

136

Palladium

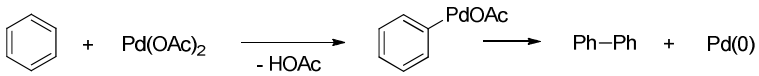


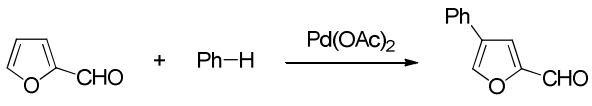
J. Tsuji, I. Shimizu, K. Yamamoto, *Tetrahedron Lett*. **1976**, *34*, 2975.

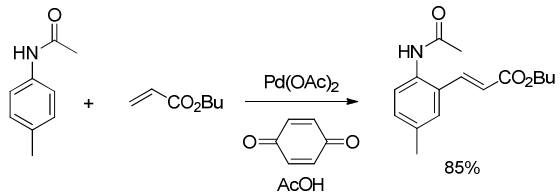
137

Palladium

C-H activation





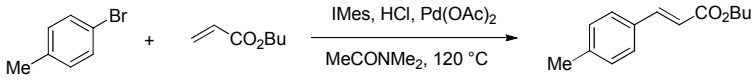


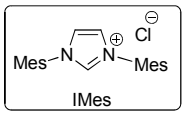
J. G. de Vries *J. Am. Chem. Soc*. **2002**, *124*, 1586

138

Palladium

Heck Reaction





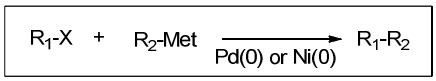
The method of T. Jeffery uses Bu_4NBr at 25 °C.

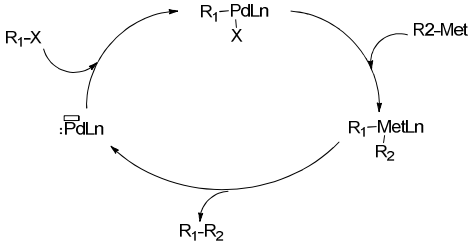
T. Jeffery *Chem. Comm.* **1984**, 1287

139

Palladium-catalyzed cross-coupling

Cross-coupling using Pd(0)-catalysts

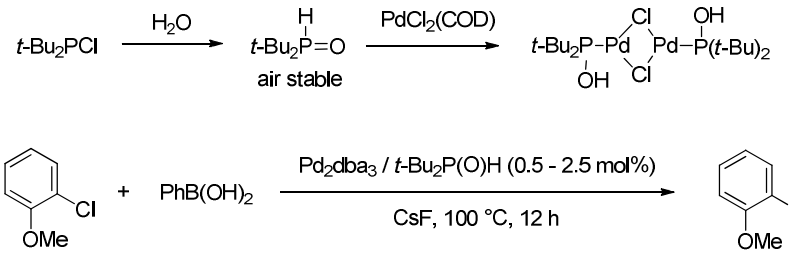




Suzuki-coupling	Met = $B(OH)_2$
Stille-coupling	Met = SnR_3
Negishi-coupling	Met = ZnX
Kumada-coupling	cat = Ni; Met = MgX
Sonogashira-coupling	Csp-Csp^2

140

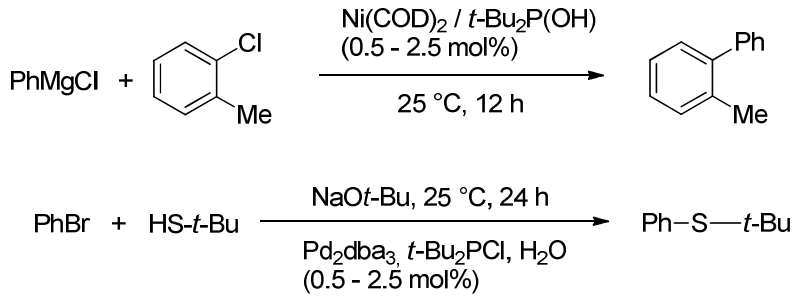
Palladium



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

141

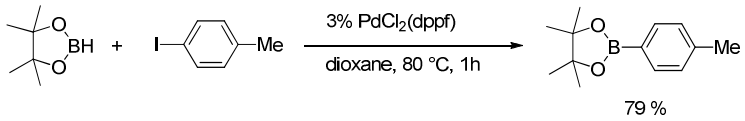
Palladium



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

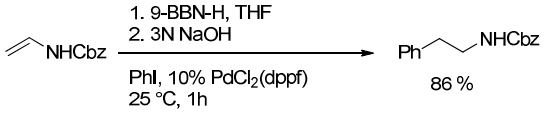
142

Palladium



79 %

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

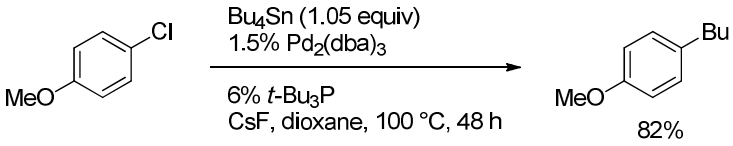


86 %

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

Palladium

Stille cross-coupling



82%

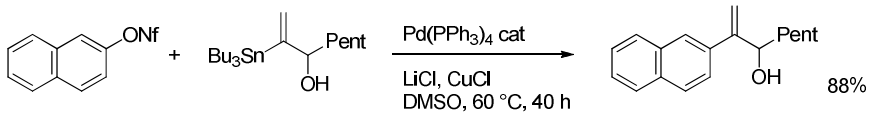
G. C. Fu, *Angew. Chem. Int. Ed.* **1999**, *38*, 2411.

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

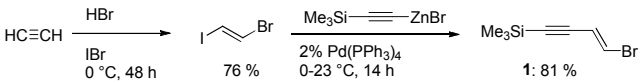


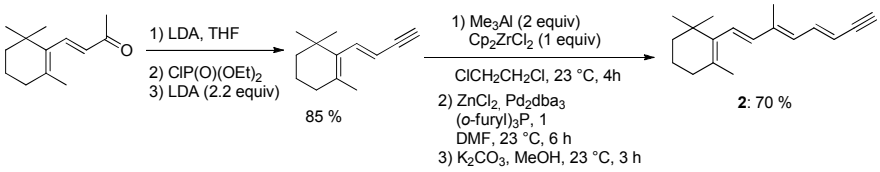
E. J. Corey, *J. Am Chem. Soc.* **1999**, *121*, 7600.

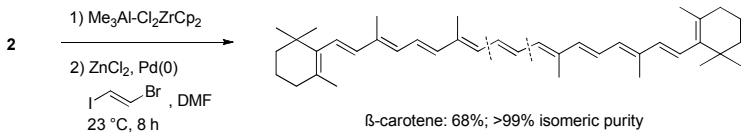
145

Negishi reactions

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





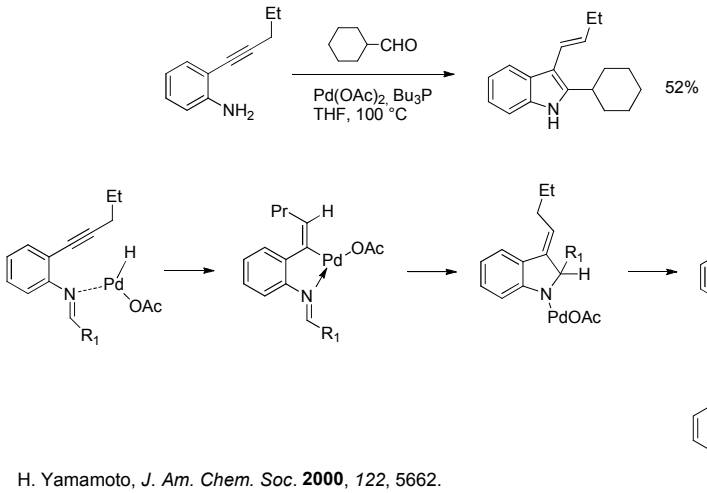


E. Negishi, *Org. Lett*. **2001**, *3*, 719.

146

Palladium

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

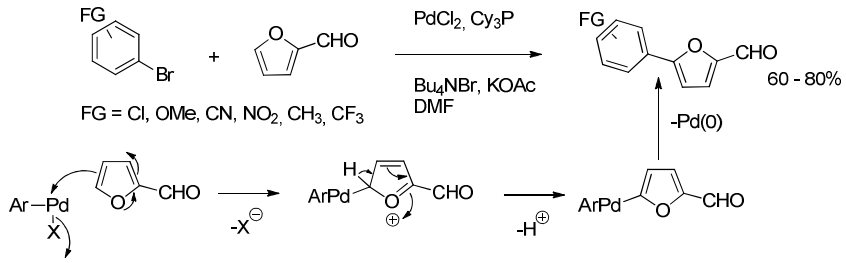


H. Yamamoto, *J. Am. Chem. Soc*. **2000**, *122*, 5662.

147

Palladium

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

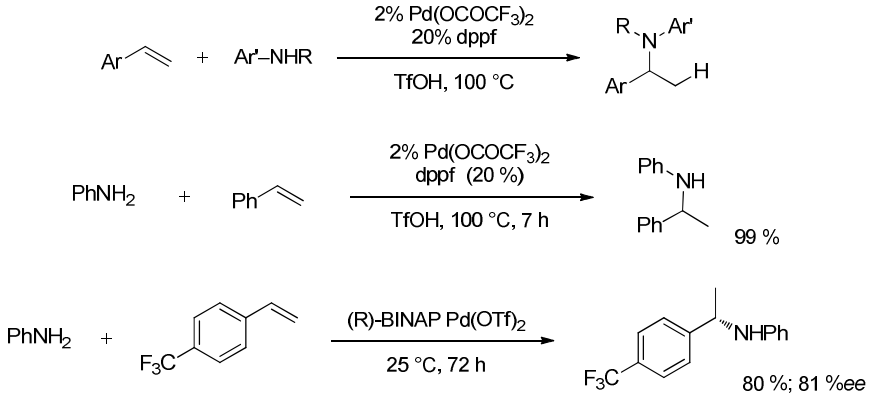


M. S. McClure, *Org. Lett*. **2001**, *3*, 1677

148

Palladium

Pd - catalyzed hydroamination of vinylarenes

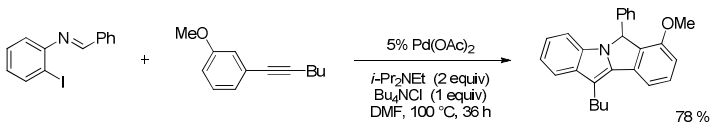


H. Hartwig *J. Am. Chem. Soc*. **2000**, *122*, 9546

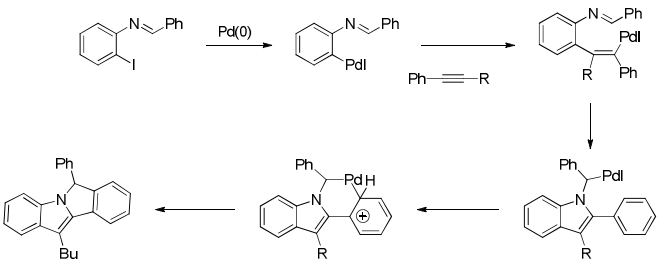
149

Palladium

Pd -catalyzed heterocycle synthesis



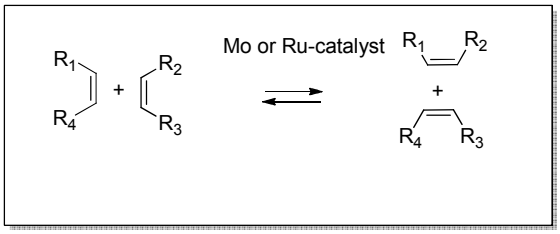
Mechanism:



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

150

Olefin metathesis

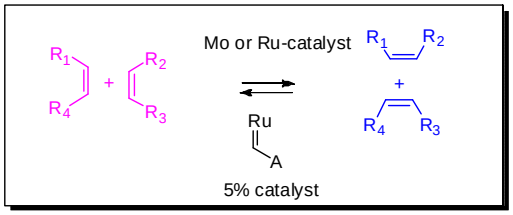


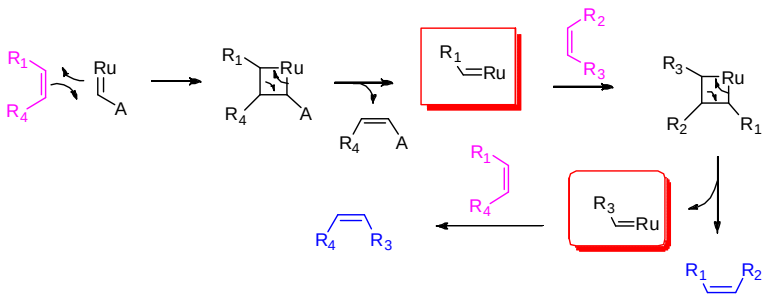
Reviews:

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 - 903.
Mechanistic study: R.H. Grubbs, J. Am. Chem. Soc. 2001, 123, 749.

151

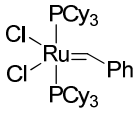
Olefin metathesis mechanism



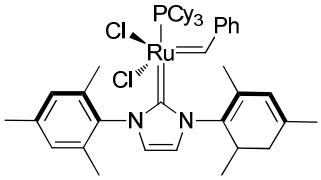


152

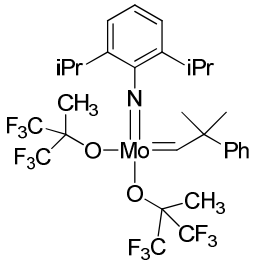
Olefin metathesis



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



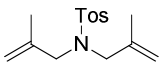
2: Grubbs-catalyst
second generation
US Patent No. 6,111,121
and 7,329,758

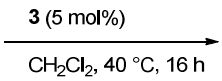


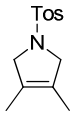
3: Schrock-catalyst
J. Am. Chem. Soc.
1998, *120*, 4041.

153

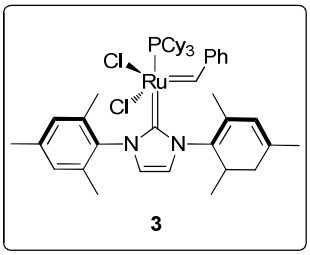
Olefin metathesis







80 %



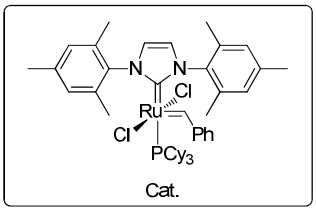
3

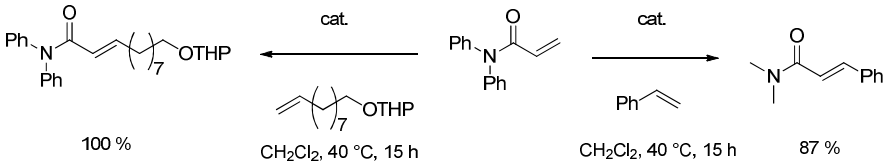
A. Fürstner, W.A. Herrmann, *Tetrahedron Lett*. **1999**, *40*, 4787

154

Olefin metathesis

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



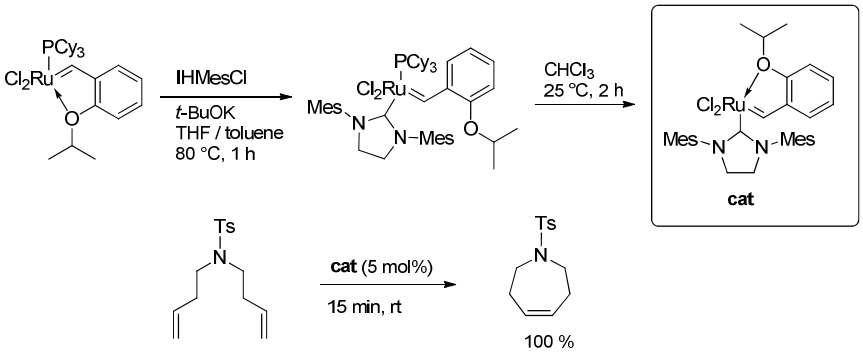


R. H. Grubbs, *Angew. Chem. Int. Ed*. **2001**, *40*, 1277

155

Olefin metathesis

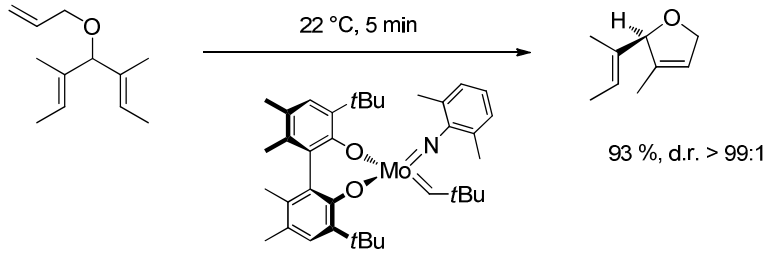
New phosphine-free metathesis catalyst



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

156

Enantioselective metathesis reaction

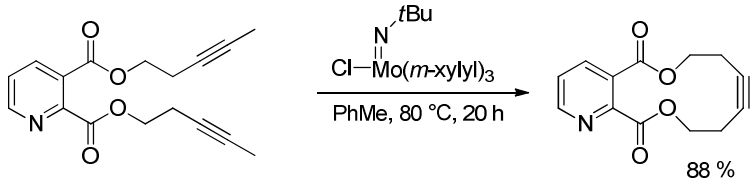


A.H. Hoveyda, R.R. Schrock, *J. Am. Chem. Soc*. **1998**, *120*, 9720
J. Am. Chem. Soc. **1999**, *121*, 8251
J. Am. Chem. Soc. **2001**, *123*, 7767

157

Olefin metathesis

Metathesis of alkynes

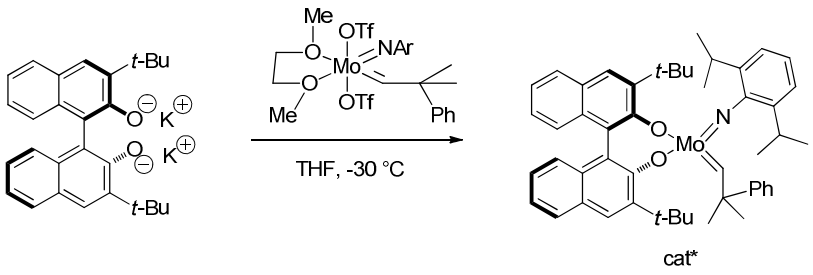


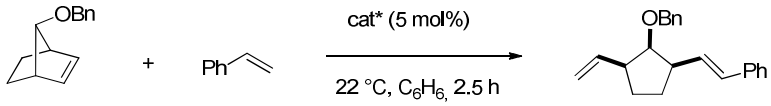
A. Fürstner, *J. Am. Chem. Soc*. **1999**, *121*, 9453.
J. Heppekausen, A. Fuerstner, *Angew. Chem. Int. Ed*. **2011**, *50*, 7829.

158

Olefin metathesis

User-friendly chiral catalyst for enantioselective olefin metathesis





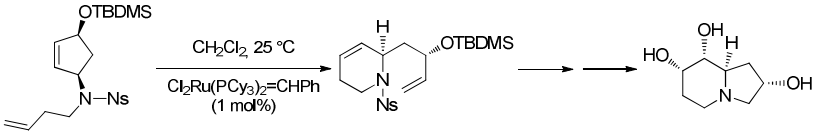
86%; >98% ee

A. H. Hoveyda, R. R. Schrock, *Angew. Chem. Int. Ed*. **2001**, *40*, 1452

159

Application to the synthesis of natural products

Synthesis of aza sugars



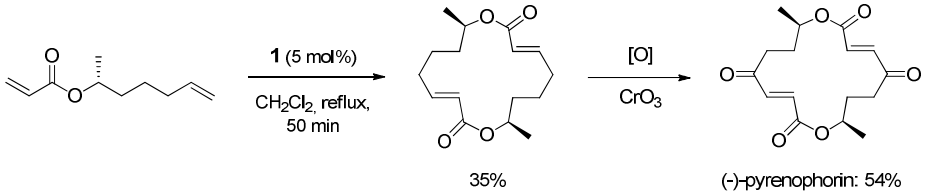
Ns = (*o*-NO_2)$C_6H_4SO_2$-

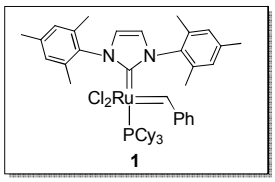
S. Blechert, *Org. Lett*. **2000**, *2*, 3971

160

Application to the synthesis of natural products

Synthesis of (*R*,*R*)-(-)-Pyrenophorin





A. Fürstner *Org. Lett*. **2001**, *3*, 449
for a new synthesis of epothilone A and C see:
A. Fürstner *Chem. Commun*. **2001**, 1057.

161

Olefin metathesis

Cross-/ self-metathesis with allylsilanes

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

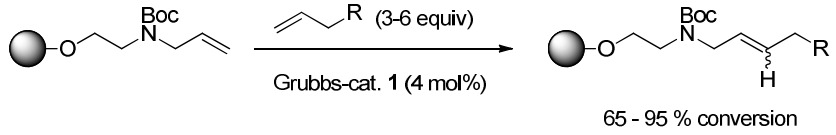
Cross-metathesis with allylic silyl ethers:
A.G.M. Barrett, *Chem. Commun*. **1996**, 2229 and 2231

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

162

Olefin metathesis

Cross metathesis with polymer bound substrates



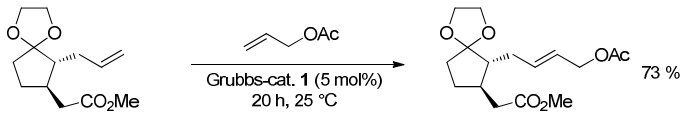
65 - 95 % conversion

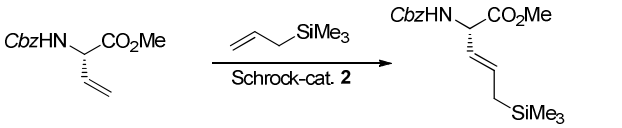
. Blechert, *Angew. Chem. Int. Ed*. **1996**, *25*, 1979; *Chem. Commun*. **1997**, 823

163

Olefin metathesis

Synthesis of jasmonic acid derivatives





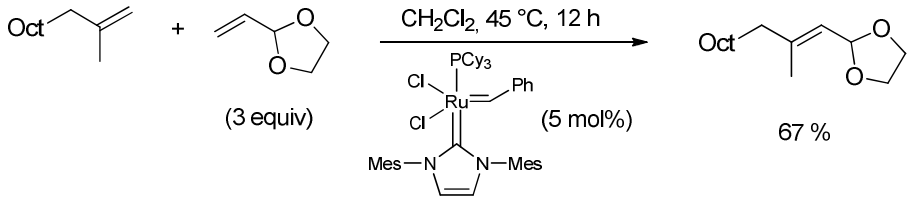
95 %, 95 %*ee*

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

164

Olefin metathesis

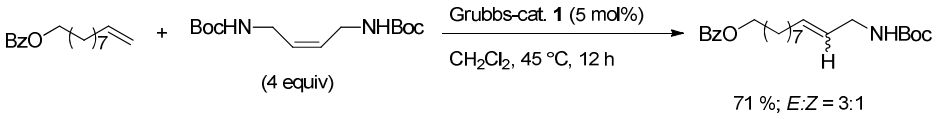
Cross-metathesis using new ruthenium carbenes



R.H. Grubbs, *Org. Lett.* **1999**, *1*, 1751
S. Blechert, *Tetrahedron Lett*. **2000**, *41*, 5465

165

Olefin metathesis

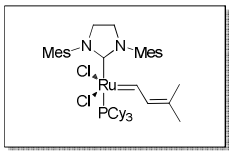


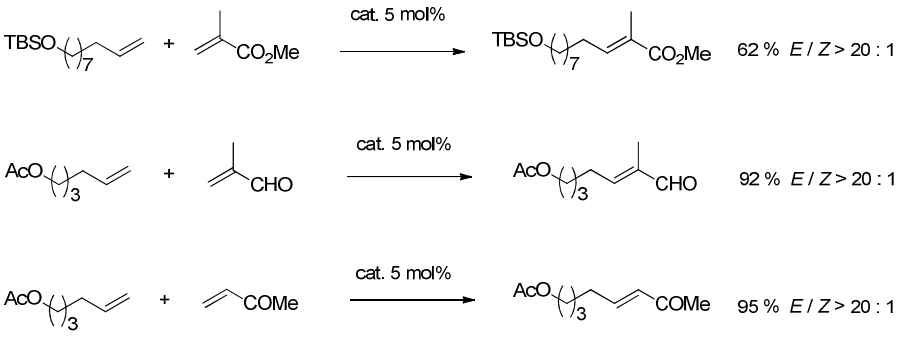
R.H. Grubbs, *Tetrahedron Lett*. **1998**, *39*, 7427

166

Olefin metathesis

Cross-metathesis using a mixed metathesis-catalyst





R. H. Grubbs, *J. Am. Chem. Soc*. **2000**, *122*, 3783

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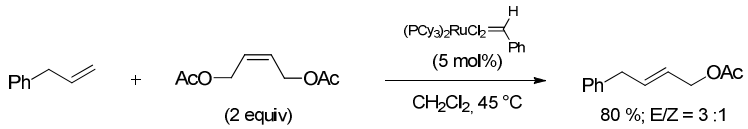
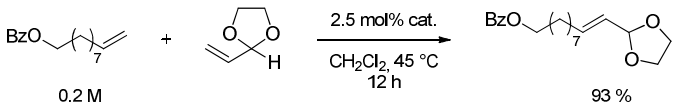
Olefin metathesis

New approaches to olefin cross – metathesis



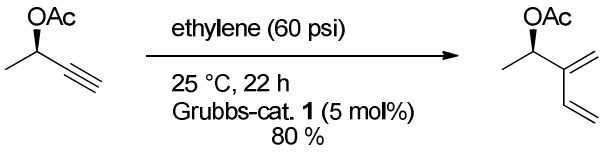


R.H. Grubbs, *J. Am. Chem. Soc*. **2000**, *122*, 58

168

Olefin metathesis

Cross-metathesis of alkynes with ethylene

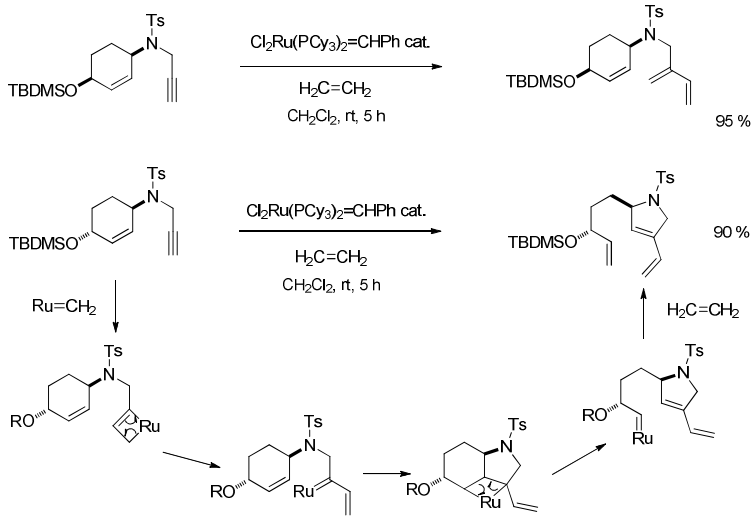


S.T. Diver, *J. Org. Chem*. **2000**, *2*, 1788

169

Olefin metathesis

Ru-catalyzed Ring-Opening and –Closing Enyne Metathesis

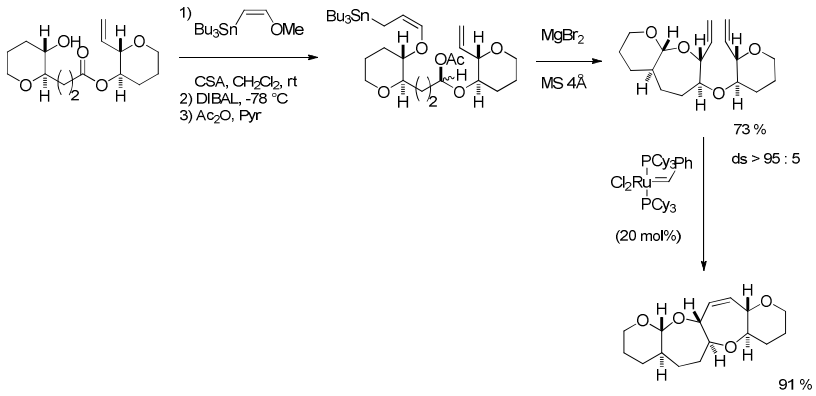


M. Mori, *Org. Lett*. **2001**, *3*, 1161

170

Olefin metathesis

Synthesis of complex ring-systems *via* metathesis

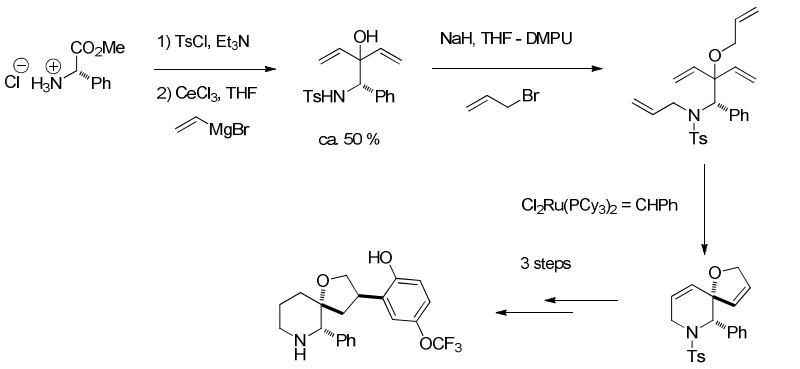


Y. Yamamoto, *J. Am. Chem. Soc*. **2001**, *123*, 6702

171

Olefin metathesis

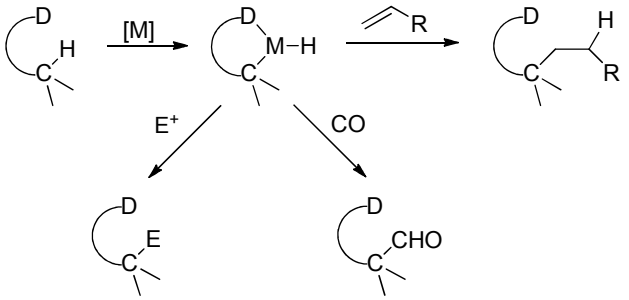
A double ring closing metathesis for the synthesis of NK-1 receptor antagonists



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

172

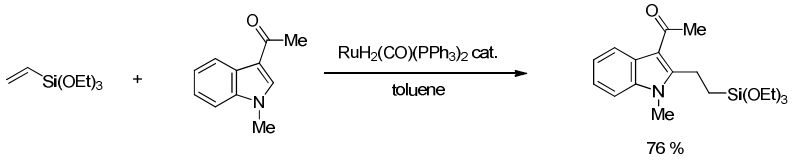
New C-H activation reactions



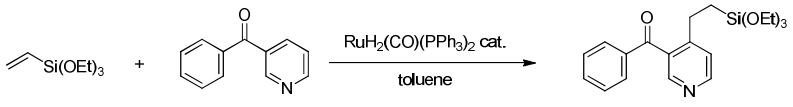
Book: S. Murai, (Ed.) Activation of Unreactive C-H Bonds in Organic Synthesis, Topics in Organometallic Chemistry, Springer, **1999**.

173

The Murai-reaction



76 %

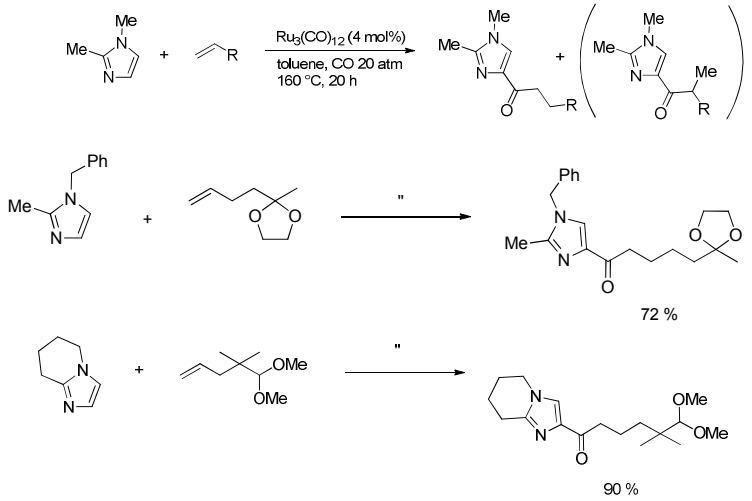


R. Grigg, *Tetrahedron Lett*. **1997**, *38*, 5737
S. Murai, *Nature*, **1993**, *366*, 529
S. Murai, *J. Organomet. Chem*. **1995**, *504*, 151

174

The Murai-reaction

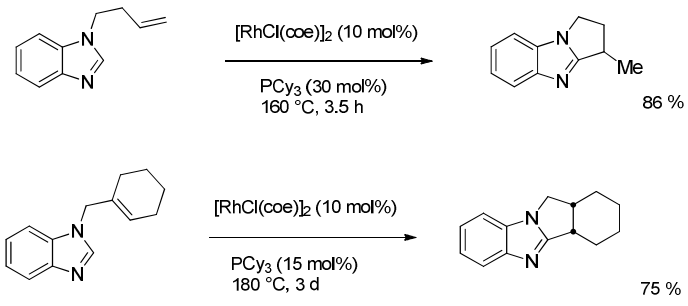
Ru-mediated synthesis of 4-acylated imidazoles *via* C-H-activation



S. Murai, *J. Am. Chem. Soc*. **1996**, *118*, 493

175

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



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

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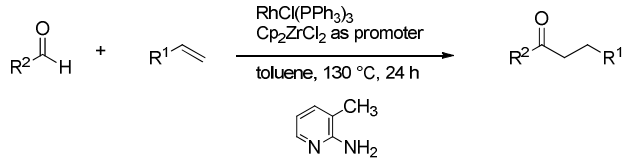
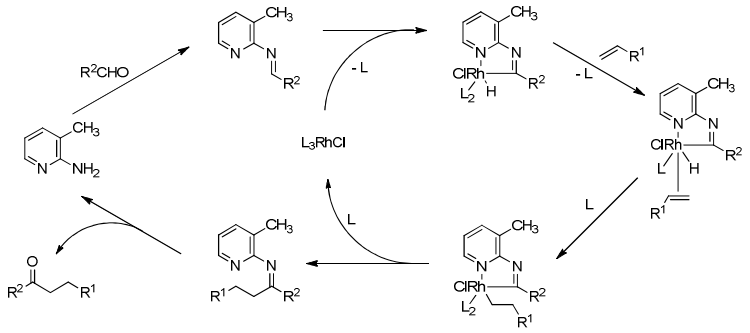
The catalytic hydroacylation of alkenes



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

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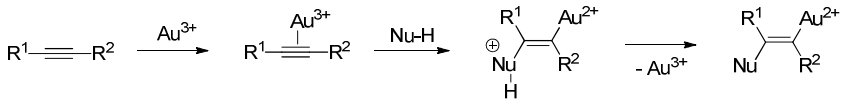
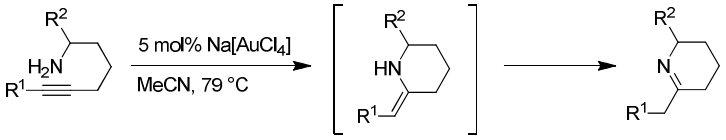
Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds





64-92%

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

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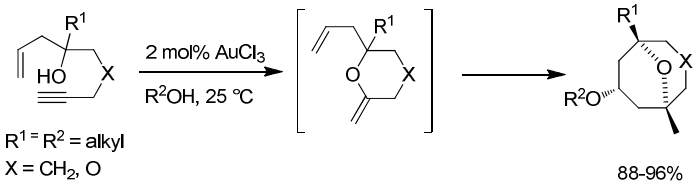
Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds:

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



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

88-96%

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

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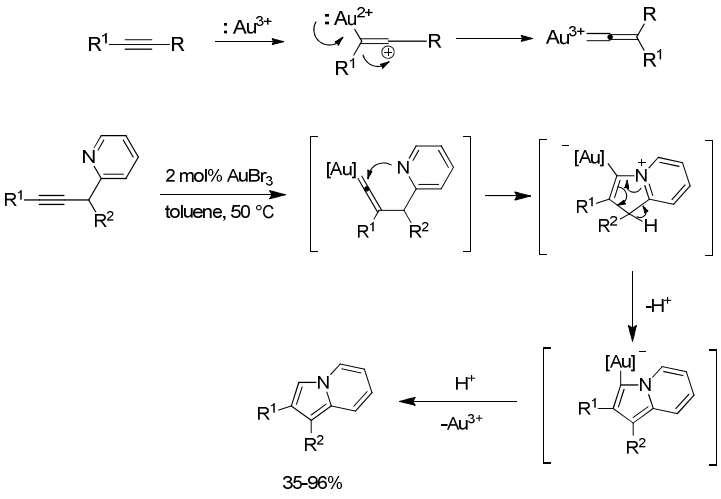
Gold-catalyzed organic reactions

Gold(III)-triggered rearrangements

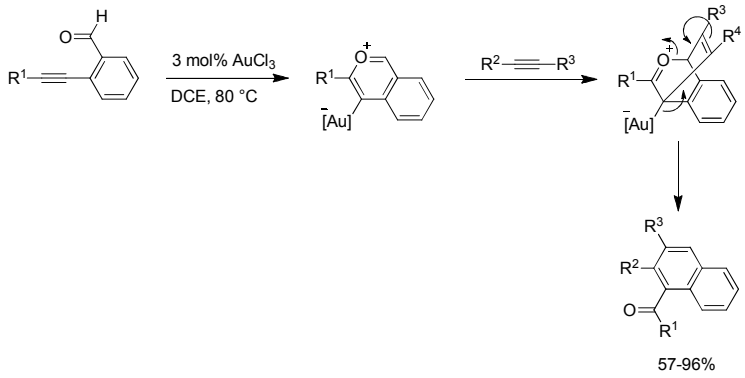


35-96%

180

Gold-catalyzed organic reactions

Au^{3+}-initiated cycloadditions



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

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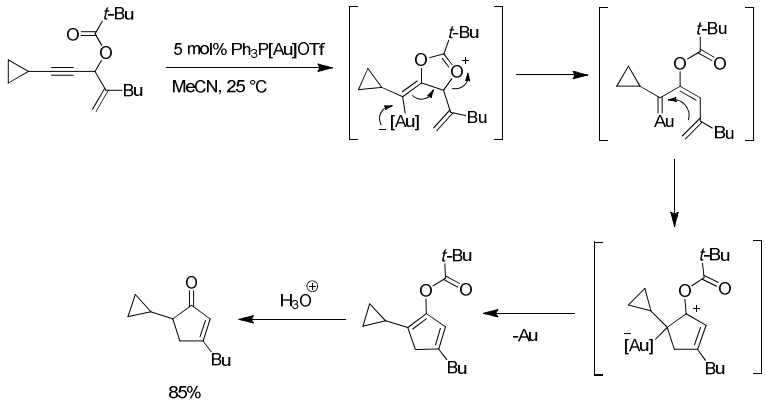
Gold-catalyzed organic reactions

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



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

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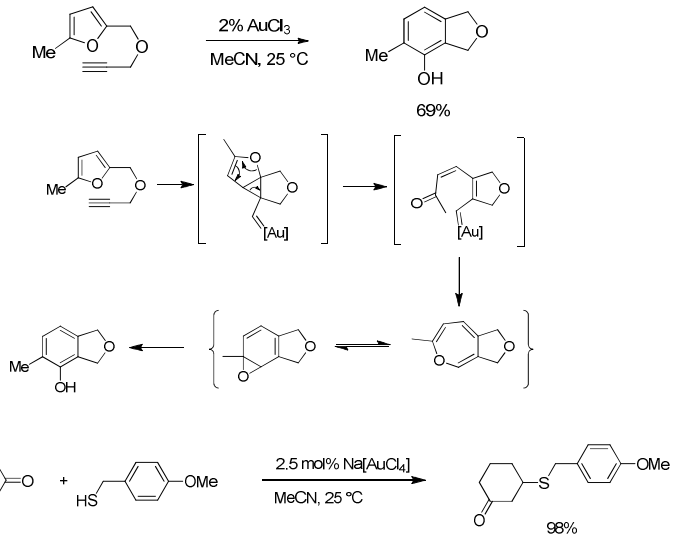
Gold-catalyzed organic reactions

Intramolecular phenol synthesis



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

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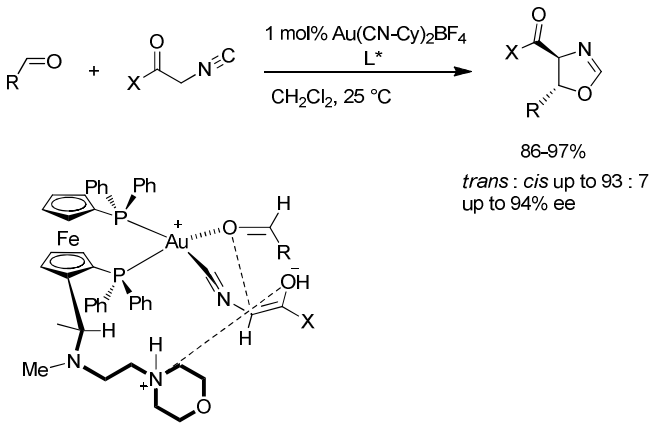
Gold-catalyzed organic reactions

Asymmetric aldol reaction



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

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