Enatioselective and Enantiospecific Transiton-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagent To Construct C-C bond

Supervisor: Prof. Huang

Reporter: Sixuan Meng

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Sarash E. Reisman *et al. Chem. Rev*. ASAP

Content

- **Introduction**
- **Enantioselective Transition-Metal-Catalyzed Alkyl Cross-Coupling Reactions**
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  - **Reactions of secondary Alkyl Electrophiles**
- **Transition-Metal-Catalyzed Enantiocontrolled Allylic Substitution**
  - **Enantioselective Allylic Substitution Reactions**

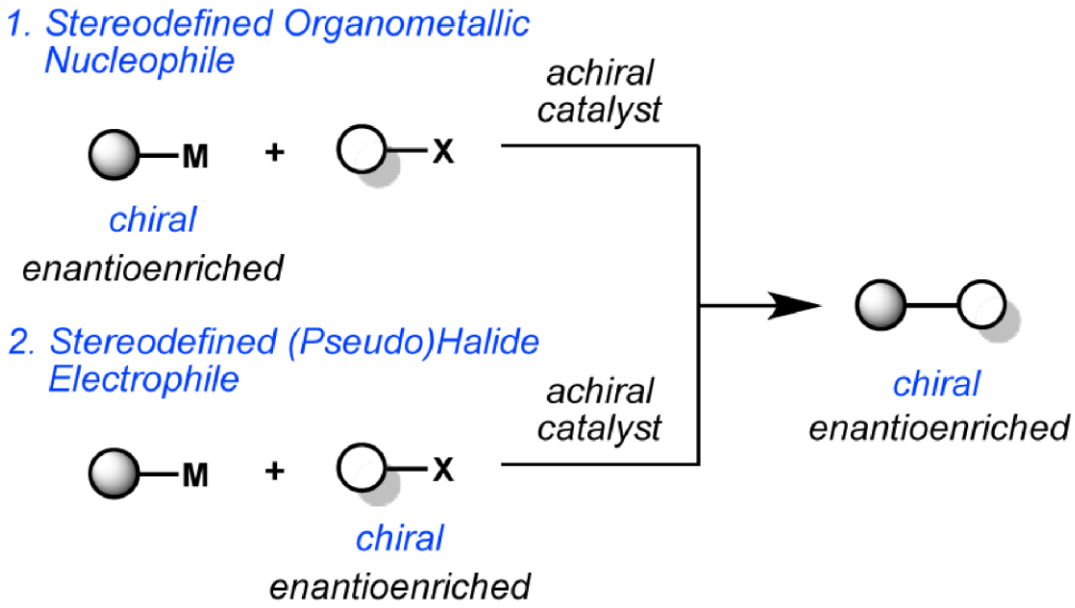
Instroduction

- **Transition-metal-catalyzed Cross-coupling Reaction**

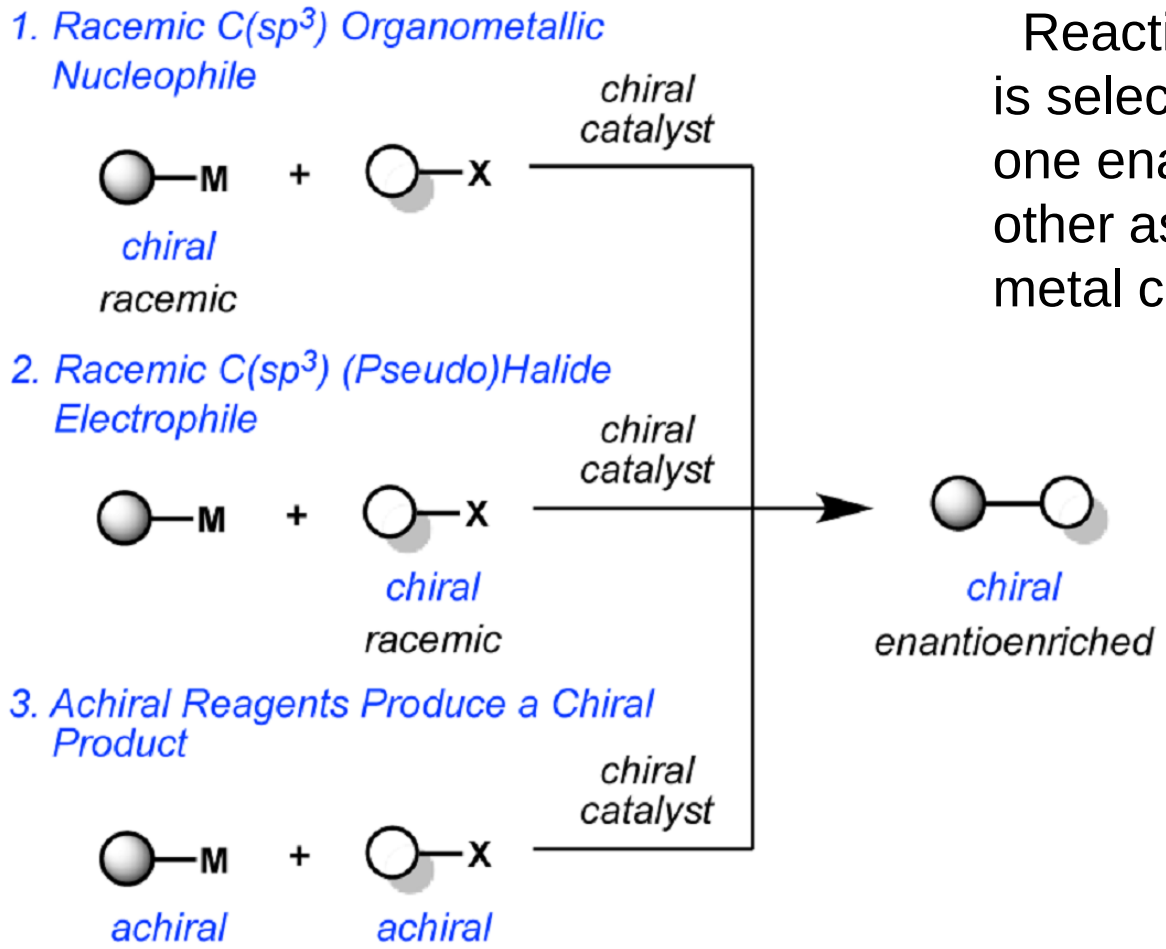
C−C bond forming reactions between an organic electrophile (typically an organic halide or pseudohalide, which in this review includes alcohols, amines, and their derivatives) and an organometallic reagent, mediated by a transition-metal catalyst.

- **Enantiospecific Cross-Coupling**

chirality exchange reactions in which the stereochemistry of a chiral, enantioenriched substrate defines the stereochemistry of the product.



- **Enantioselective Cross-Coupling**



Reactions in which there is selective formation of one enantiomer over the other as defined by a chiral metal catalyst.

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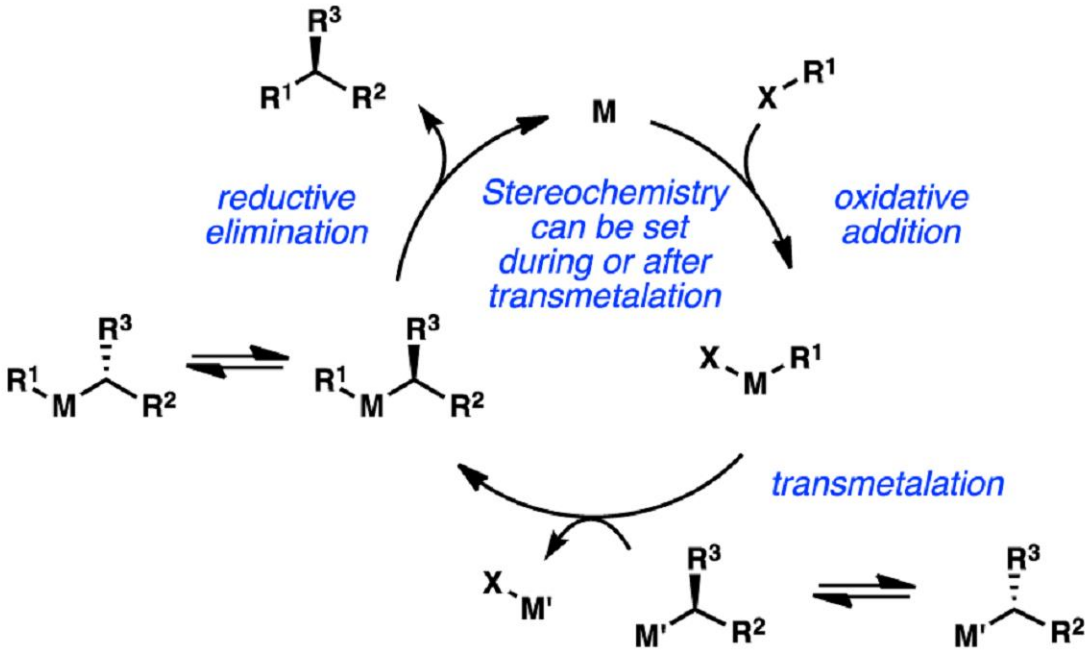
  - **Reactions of secondary Alkylmetallic Reagents**
  - **Reactions of secondary Alkyl Electrophiles**
- **Transition-Metal-Catalyzed Enantiocontrolled Allylic Substitution**
  - **Enantioselective Allylic Substitution Reactions**

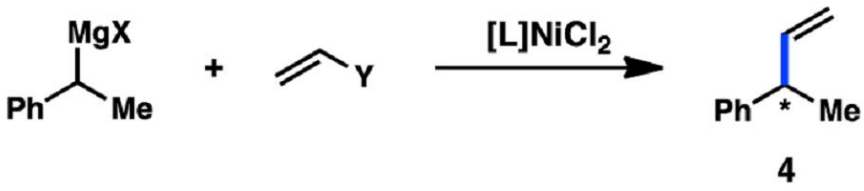
Enantioselective Transition-Metal-Catalyzed Alkyl Cross-Coupling Reactions

- **Reactions of secondary Alkylmetallic Reagents**

In principle, fast equilibration between the two enantiomers of a *sec*-alkylmetallic reagent or between two diastereomers of a chiral transition metal complex could enable enantioselective cross-coupling through a dynamic kinetic asymmetric transformation (DYKAT)



Organomagnesium Reagent



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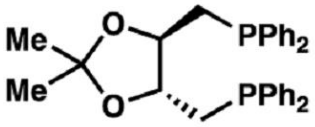
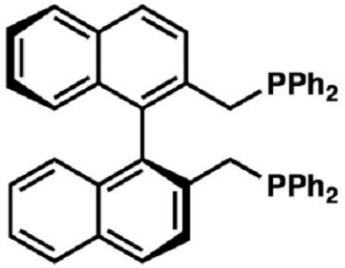


DIOP (L1)
(Kumada, 1974)

X = Cl, Y = Cl

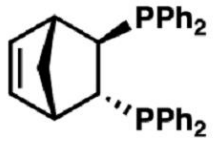
81% yield, 13% ee



Naphos (L6)
(Kumada, 1977)

X = Cl, Y = Br

11% ee

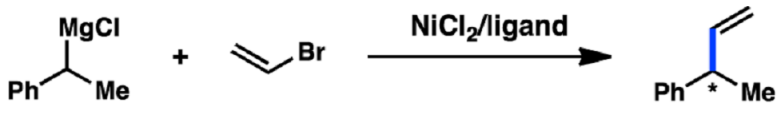


Norphos (L4)
(Brunner, 1981)

X = Cl, Y = Br

95% yield, 67% ee

Kumada, M. *et al. Tetrahedron Lett*. **1974**, *15*, 3
Kumada, M. *et al. Tetrahedron Lett*. **1977**, *18*, 1389
Brunner, H. *et al. J. Organomet. Chem*. **1981**, *209*, C1



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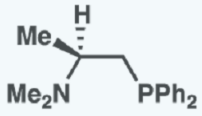
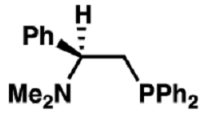


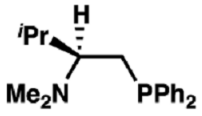
L7

98% yield, 38% ee



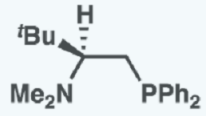
L8

97% yield, 70% ee



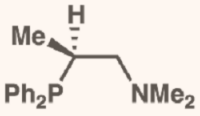
L9

96% yield, 81% ee



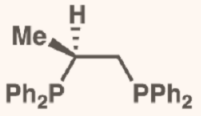
L10

96% yield, 94% ee



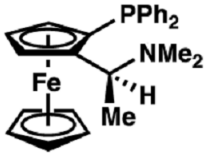
L11

97% yield, 25% ee



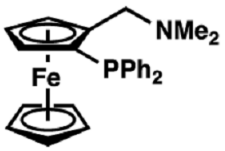
L12

98% yield, 0% ee



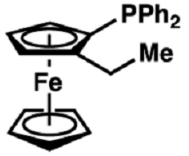
PPFA (L13)

99% yield, 63% ee



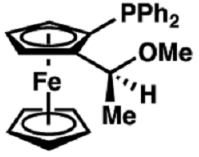
FcPN (L14)

98% yield, 60% ee



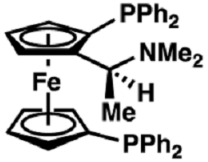
EPPF (L15)

86% yield, 4% ee



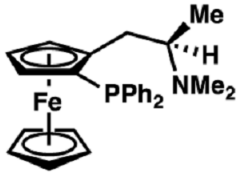
L16

95% yield, 57% ee



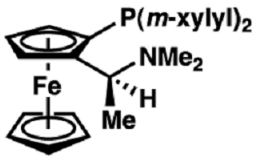
BPPFA (L17)

73% yield, 65% ee



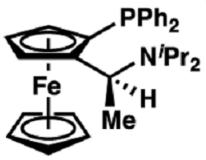
L18

88% yield, 18% ee



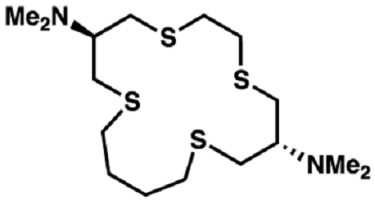
L19

90% yield, 65% ee



L20

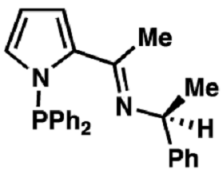
49% yield, 7% ee



L21

46% yield, 50% ee

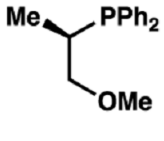
(Kellogg, 1984)



L22

66% yield, 32% ee

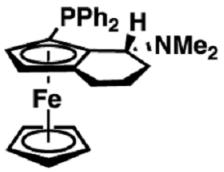
(Brunner, 1985)



L23

68% ee

(Brunner, 1996)



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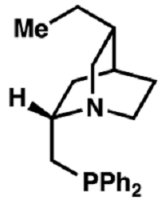
95% yield, 79% ee

(w/ Pd catalyst)

(Weissensteiner, 1993)

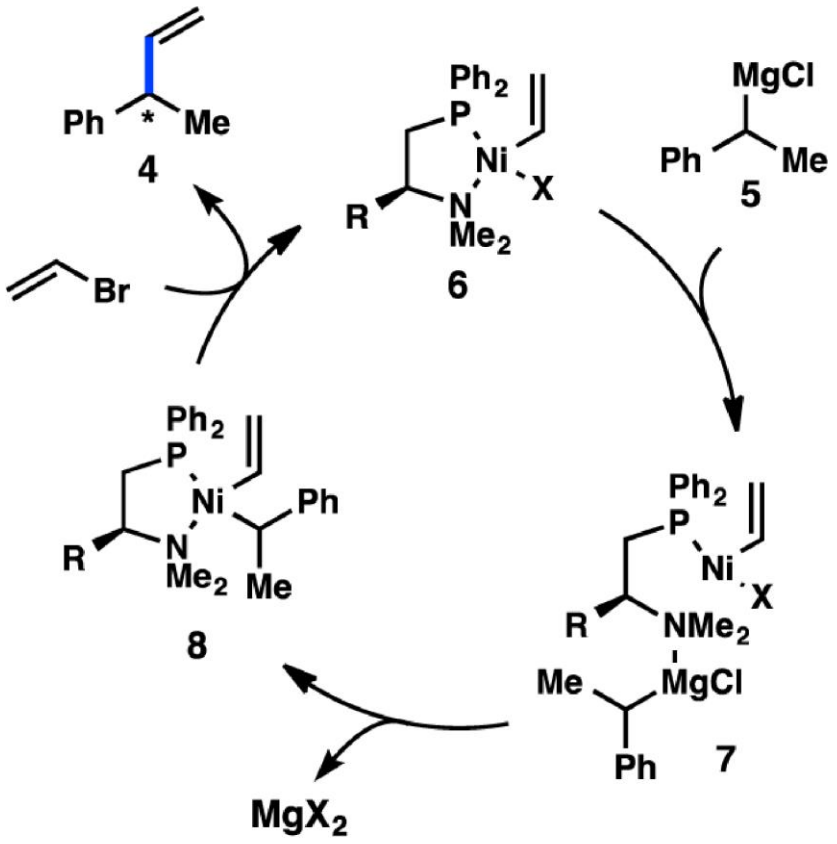


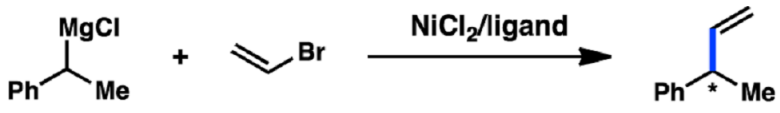
L25

50% yield, 85% ee

(Lemaire, 2001)

- Proposed catalytic cycle for the enantioselective coupling of α-methylbenzyl Grignard reagents





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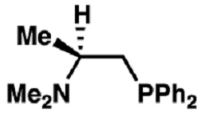

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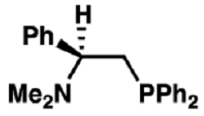

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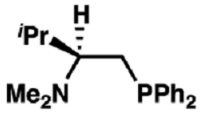

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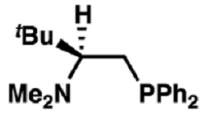

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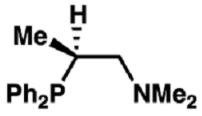
96% yield, 94% ee



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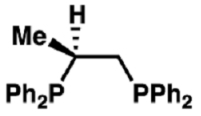

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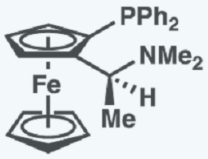
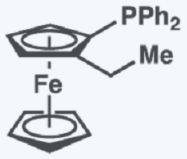


PPFA (L13)
99% yield, 63% ee

FcPN (L14)
98% yield, 60% ee



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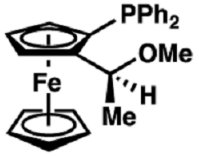

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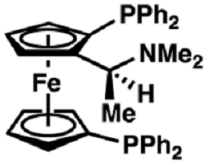
95% yield, 57% ee



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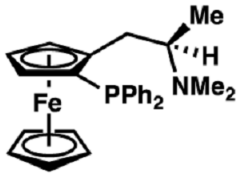
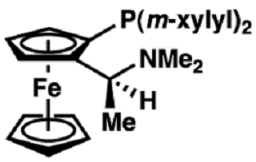
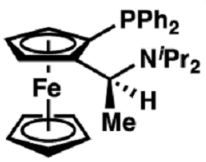


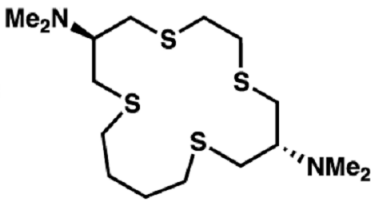
L18
88% yield, 18% ee



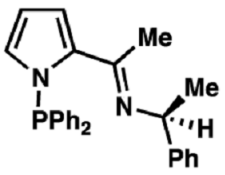
L19
90% yield, 65% ee



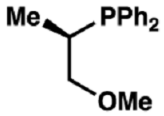
L20
49% yield, 7% ee



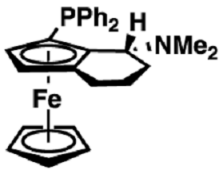
L21
46% yield, 50% ee
(Kellogg, 1984)



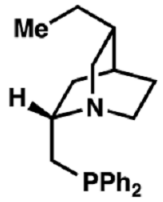
L22
66% yield, 32% ee
(Brunner, 1985)



L23
68% ee
(Brunner, 1996)

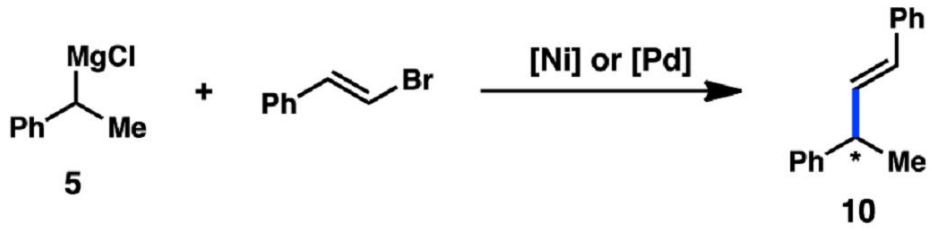


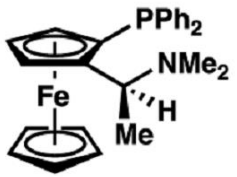
L24
95% yield, 79% ee
(w/ Pd catalyst)
(Weissensteiner, 1993)



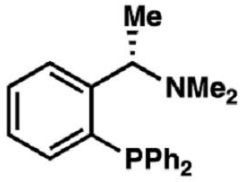
L25
50% yield, 85% ee
(Lemaire, 2001)

- Coupling of disubstituted alkenes

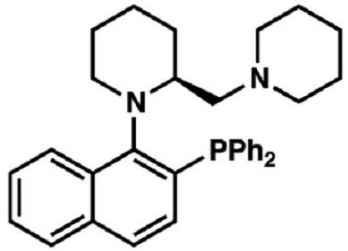




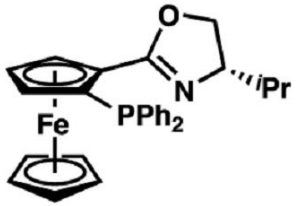
PPFA (L13) w/ [Ni]
(Kumada, 1981)
62% yield, 52% ee



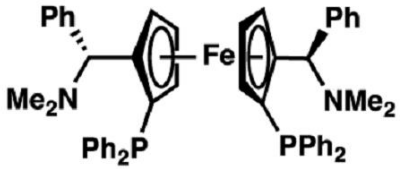
L27 w/ [Pd]
(Kreuzfeld, 1987)
95% yield, 40% ee



L28 w/ [Pd]
(Aoyama, 2003)
64% yield, 76% ee



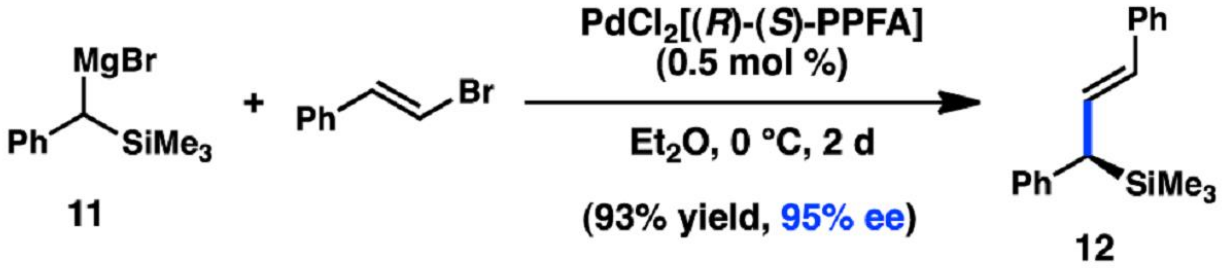
L29 w/ [Pd]
(Richards, 1995)
74% yield, 45% ee



L30 w/ [Pd]
(Knochel, 1998)
89% yield, 93% ee

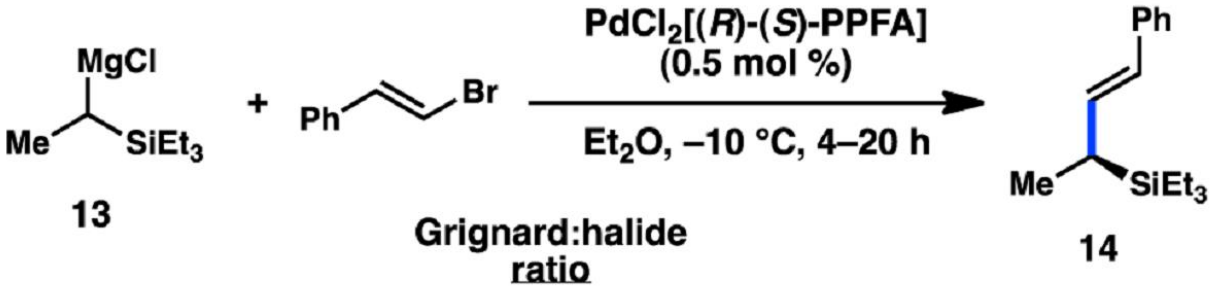
- Coupling of α-Silyl Grignard Reagents

a) Coupling of α-phenyl-α-trimethylsilyl Grignard reagents



Kumada, M. *et al.* *J. Org. Chem*. **1986**, *51*, 3772

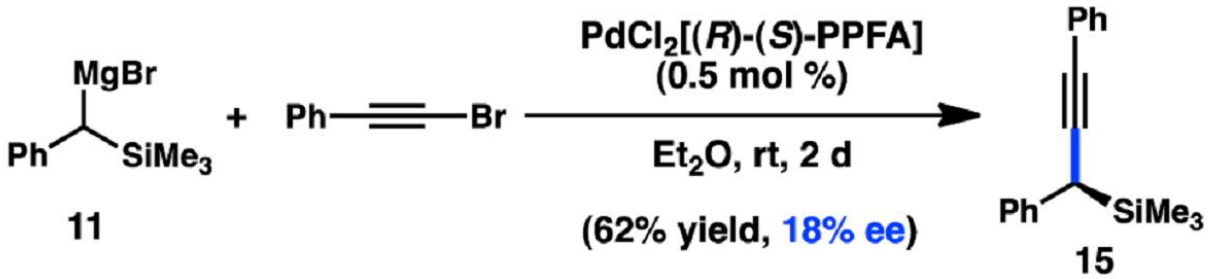
b) Coupling of α-alkyl-α-triethylsilyl Grignard reagents



Grignard:halide ratio	
2:1	(88% yield, 93% ee)
0.86:1	(93% yield, 14% ee)

Kumada, M. *et al.* *Tetrahedron Lett*. **1981**, *22*, 137

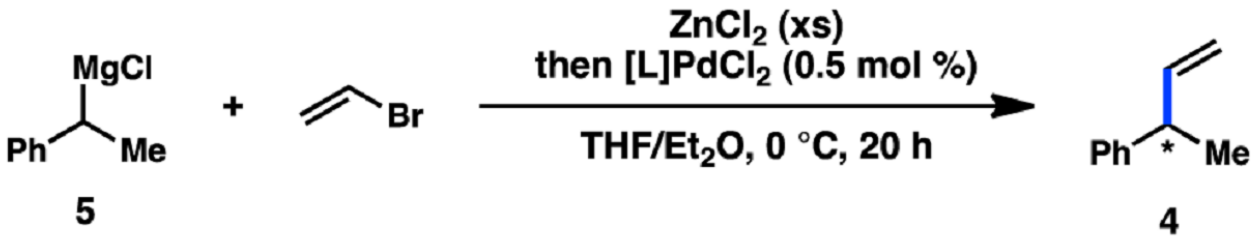
c) Alkynylation of α-phenyl-α-trimethylsilyl Grignard reagents

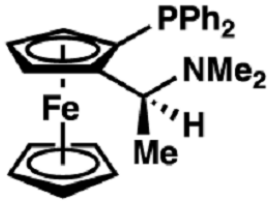


Kumada, M. *et al.* *Tetrahedron Lett*. **1983**, *24*, 807

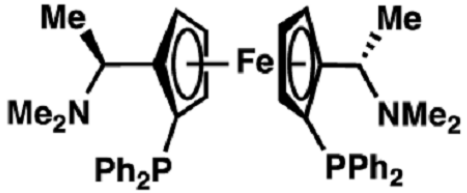
Organozinc Reagent (Negishi-type)

a) Cross-coupling of vinyl electrophiles





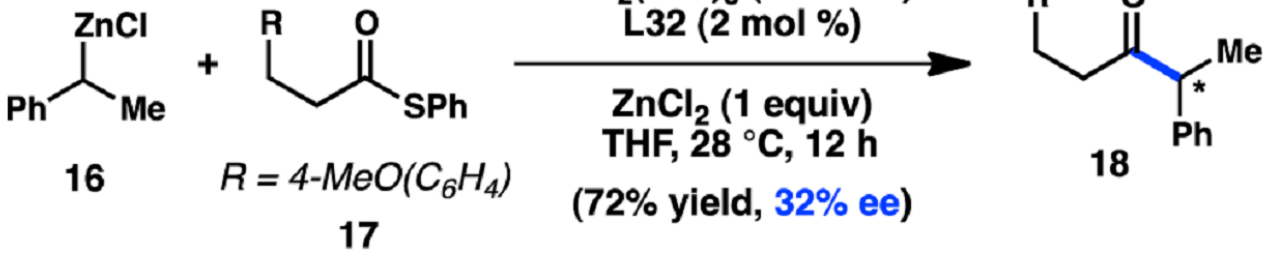
PPFA (L13)
>95% yield, 85% ee

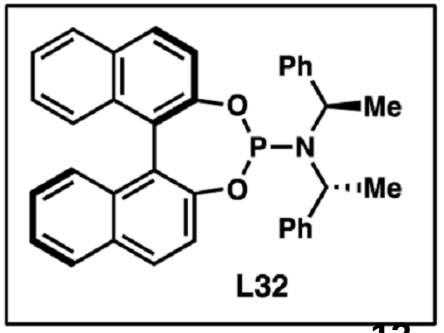


L31
quant. yield, 93% ee

Ito, Y. *et al. Chem. Commun*. **1989,** 495

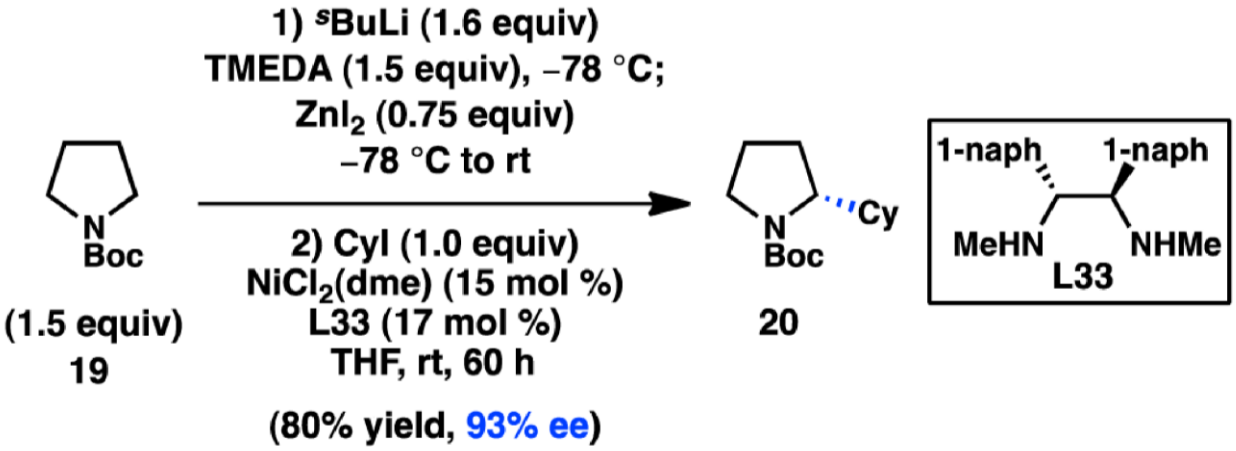
b) Cross-coupling of acyl electrophiles

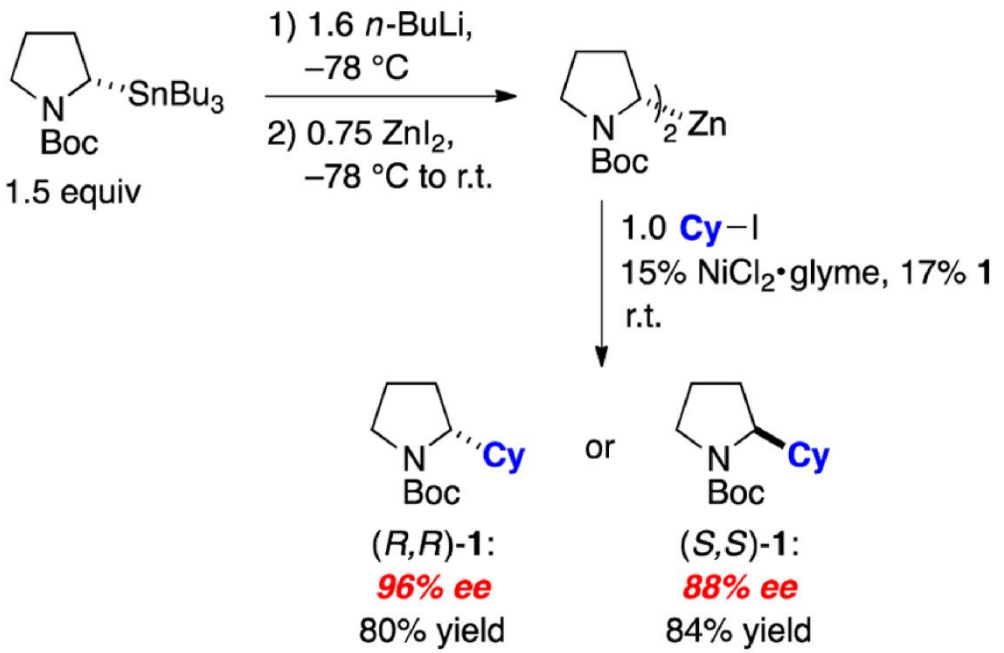


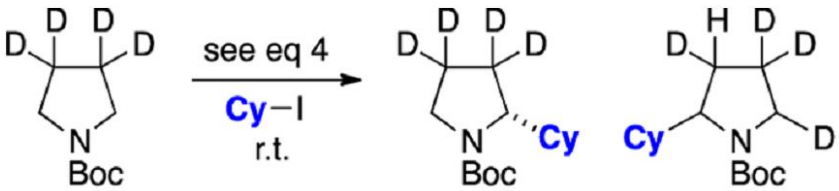


Reisman, S. E. *et al. Tetrahedron* **2014,** *70,* 3259

- Enantioconvergent alkyl-alkyl coupling



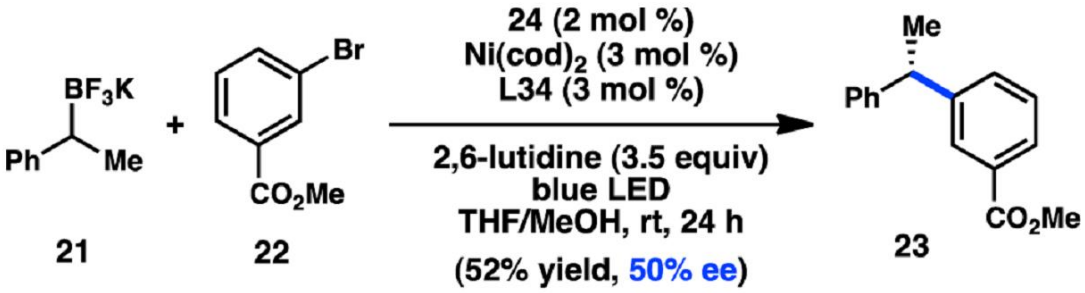


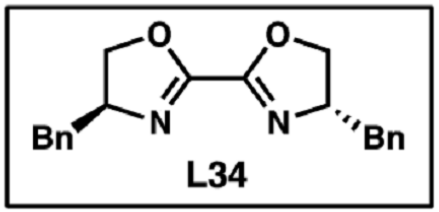


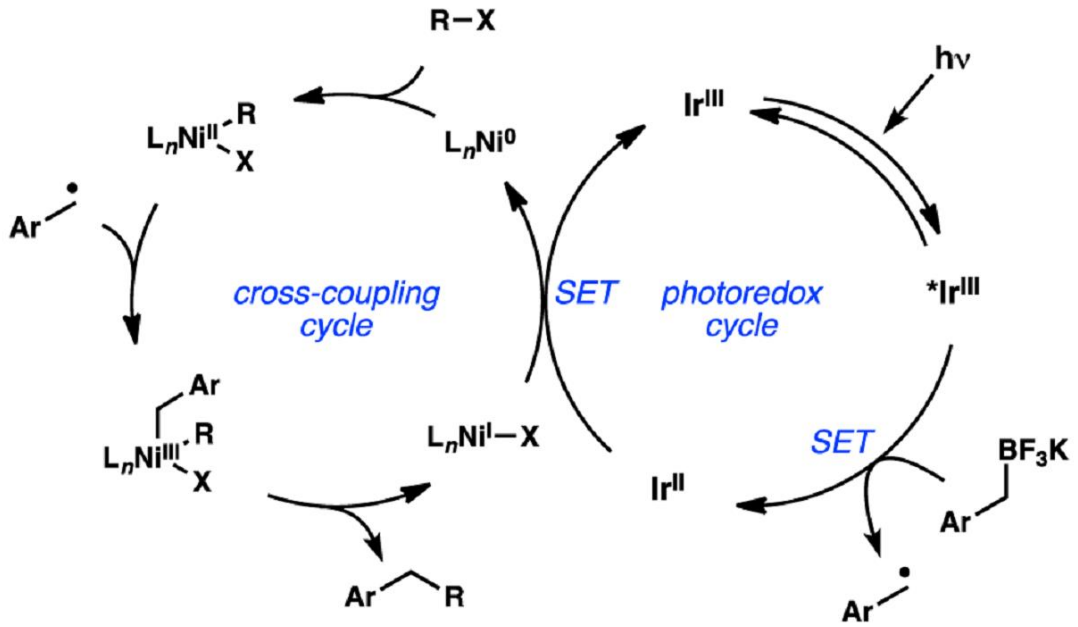
Fu, G. C. *et al. J. Am. Chem. Soc*. **2013**, *135*, 10946

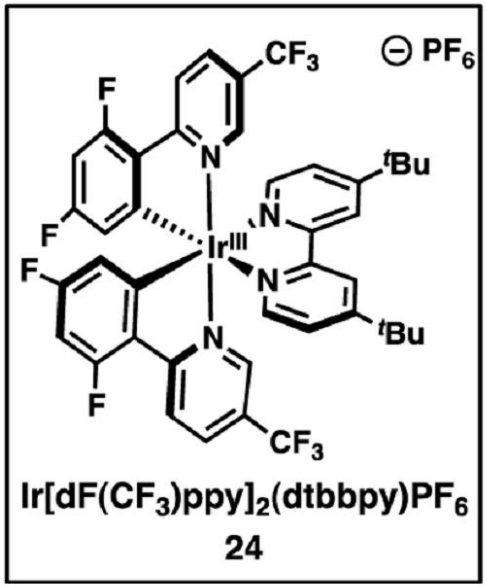
Organoboron Reagents

- **Dual catalysis approach to asymmetric cross-coupling**









Molander, G. A. *et al. Science* **2014**, *345*, 433

Reactions of secondary Alkyl electrophiles

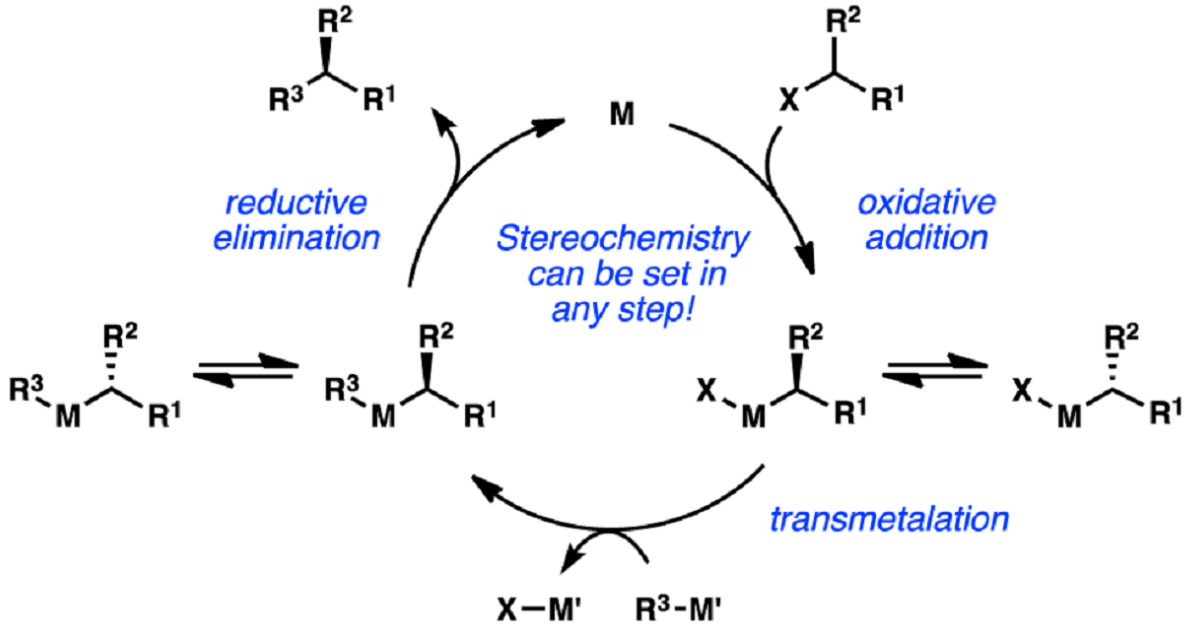
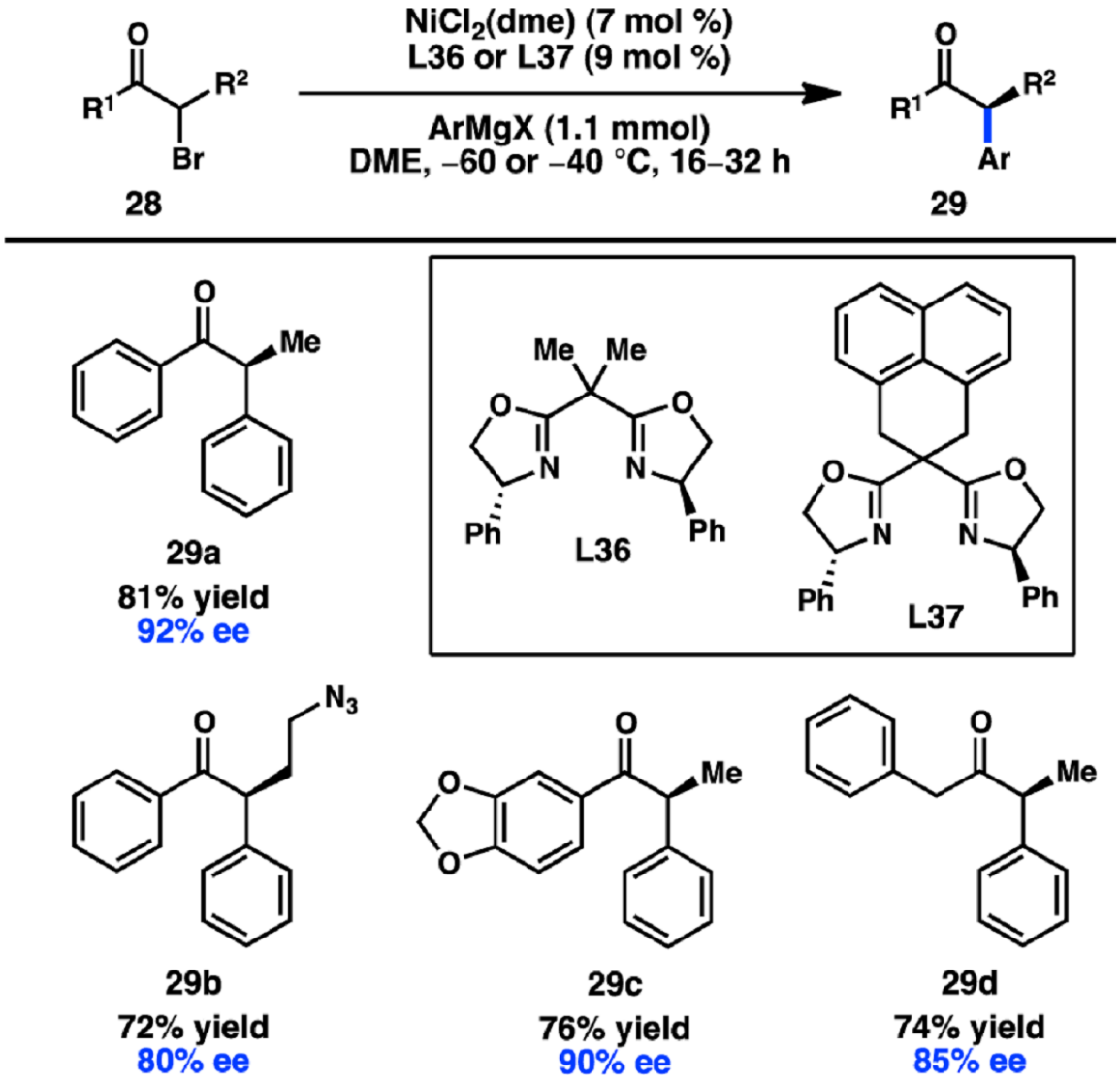


Figure 12. Stereochemical outcome of cross-coupling with secondary electrophiles.

With Organomagnesium Reagent (Kumada-Corriu)

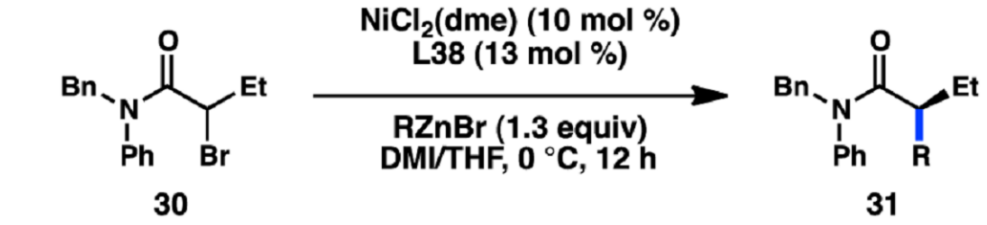


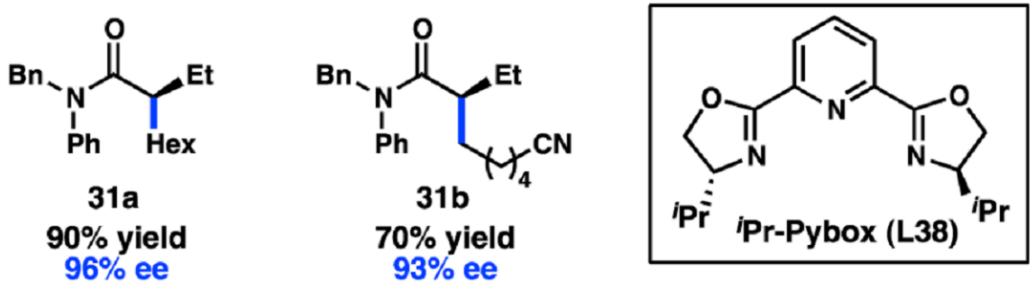
Fu, G. C. *et al. J. Am. Chem. Soc*. **2010**, *132,* 1264

With Organozinc Reagent (Negishi)

Alkylzinc Reagent

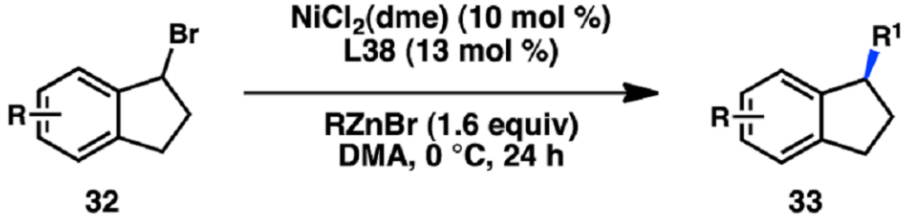
a) Negishi coupling of α-bromo amides

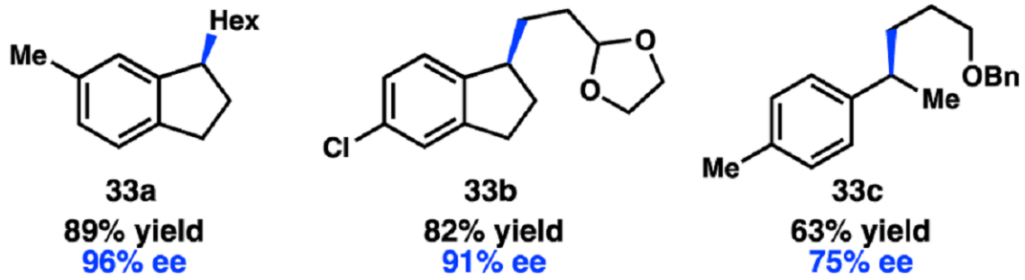




Fu, G. C. *et al. J. Am. Chem. Soc*. **2005**, *127*, 4594

b) Negishi coupling of benzyl halides

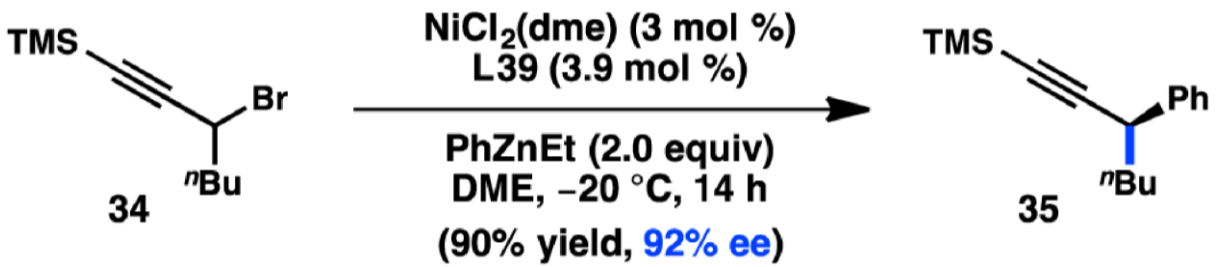


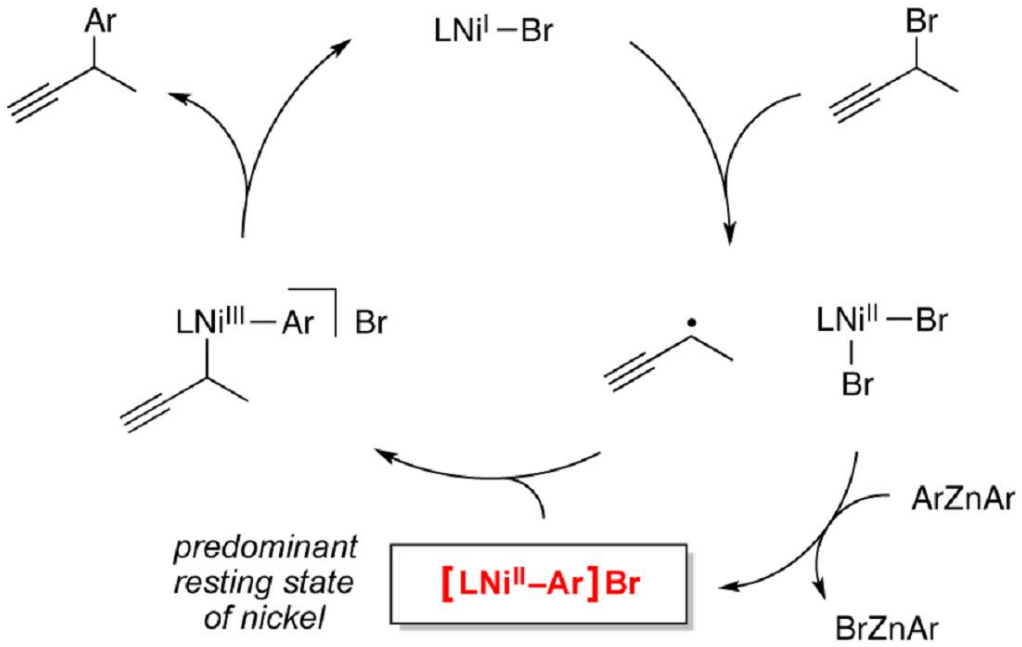


Fu, G. C. *et al. J. Am. Chem. Soc*. **2005**, *127*, 10482

Arylzinc Reagent

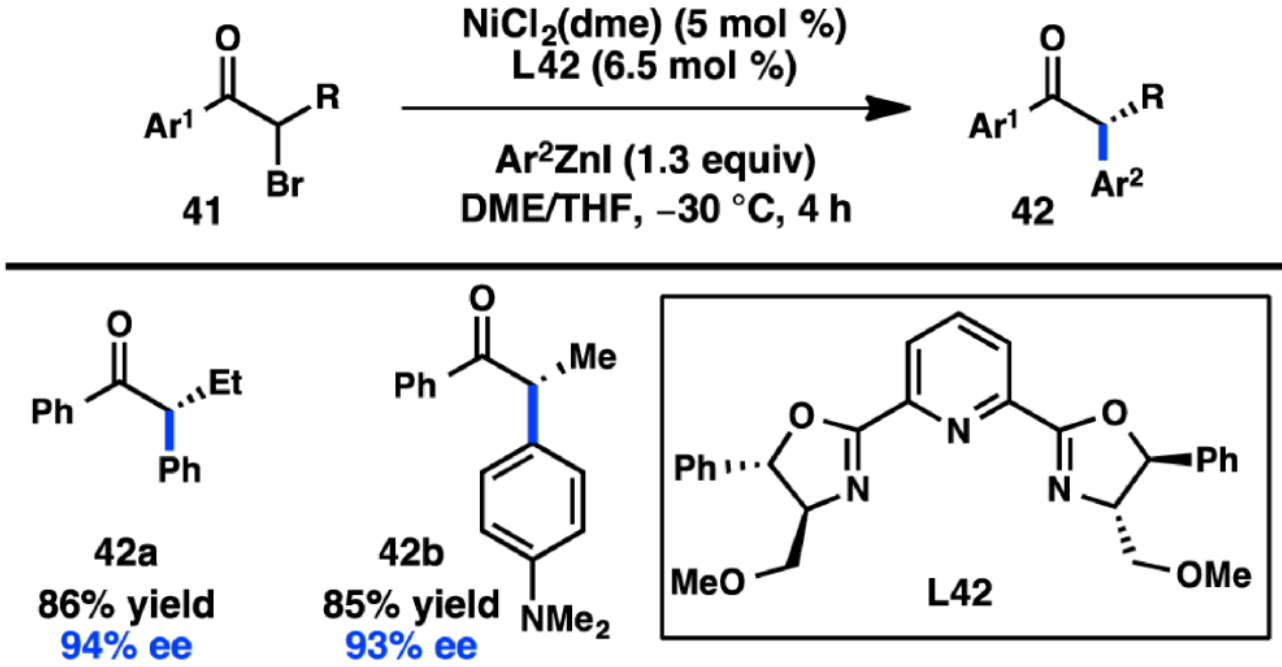
a) Negishi cross-coupling of propargyl halides





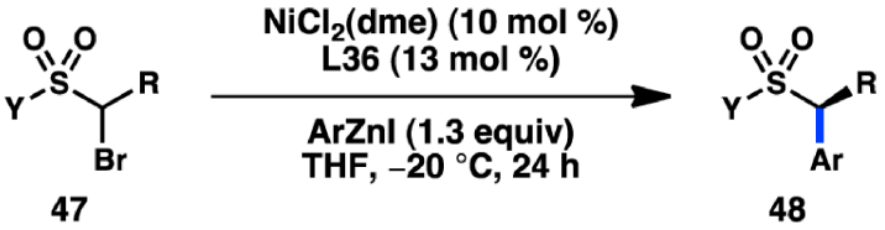
Fu, G. C. *et al. J. Am. Chem. Soc*. **2008**, *130*, 12645

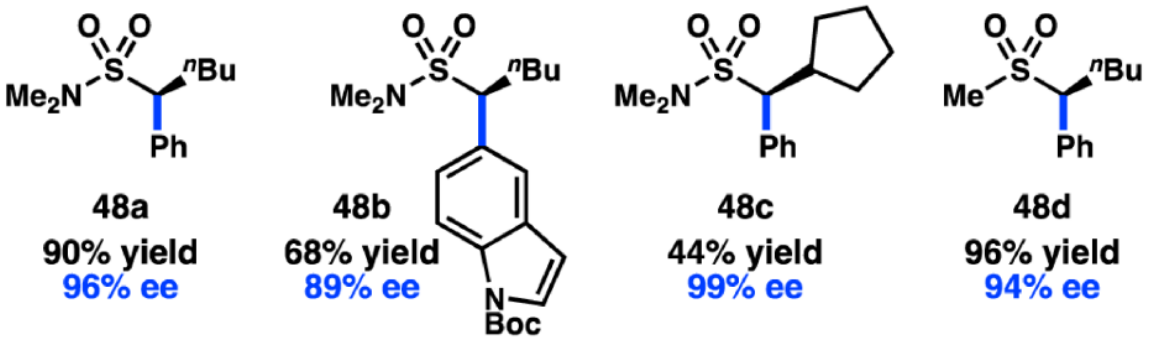
a) Negishi cross-coupling of α-bromo ketones

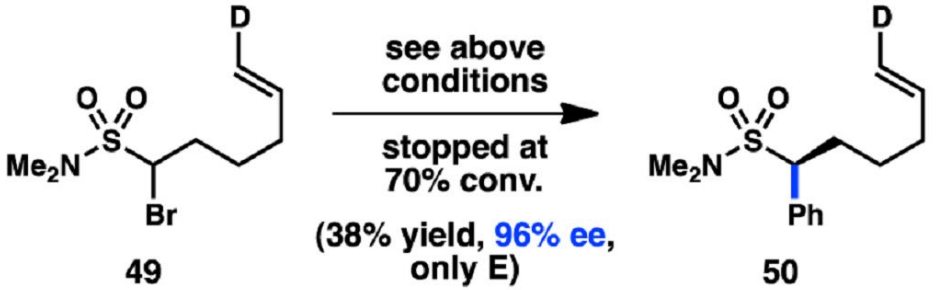


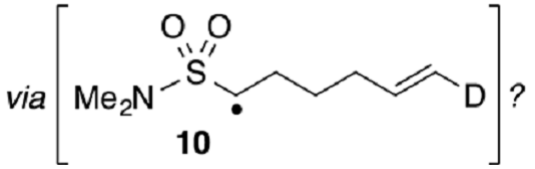
Fu, G. C. *et al. Angew. Chem. Int. Ed.*, **2009**, *48*, 154

b) Negishi cross-coupling of α-halosulfonamides and sulfones

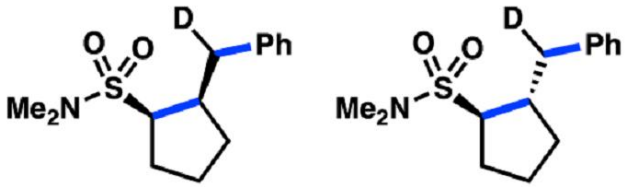








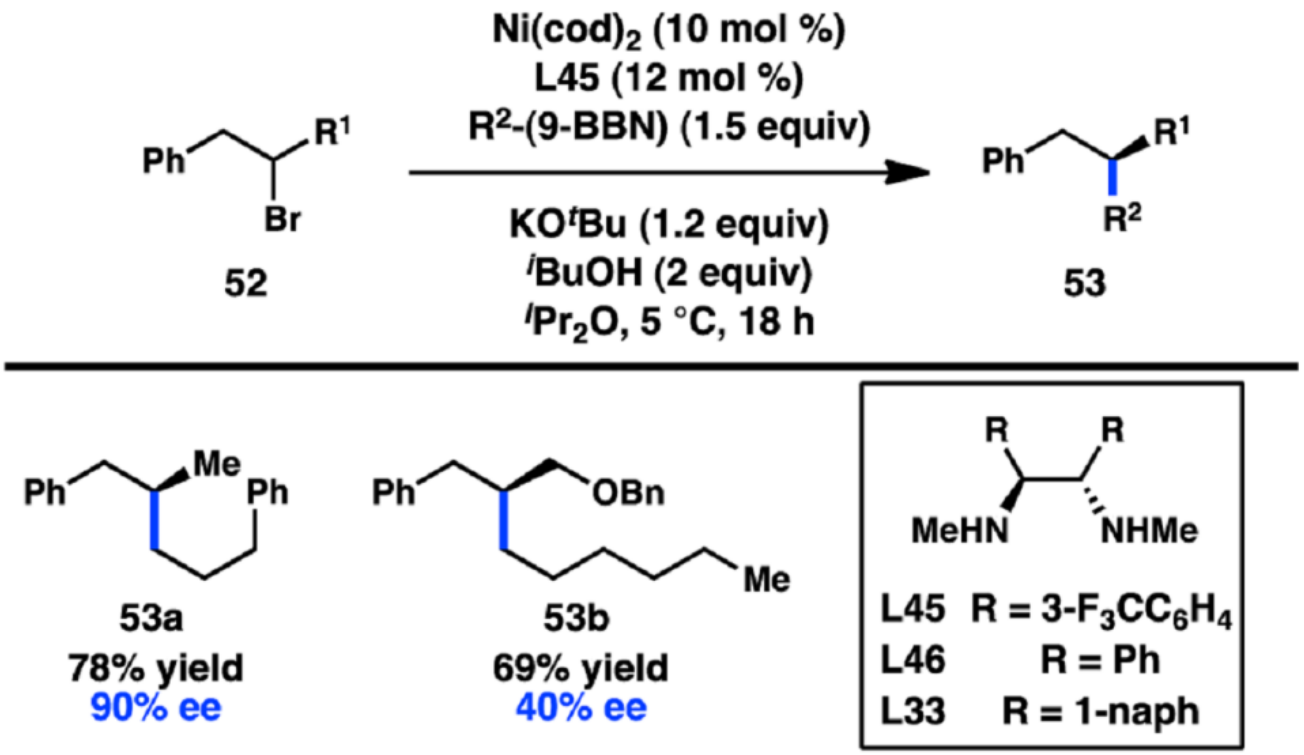
side products:



Fu, G. C. *et al. JACS.* **2014**, *136*, 12161

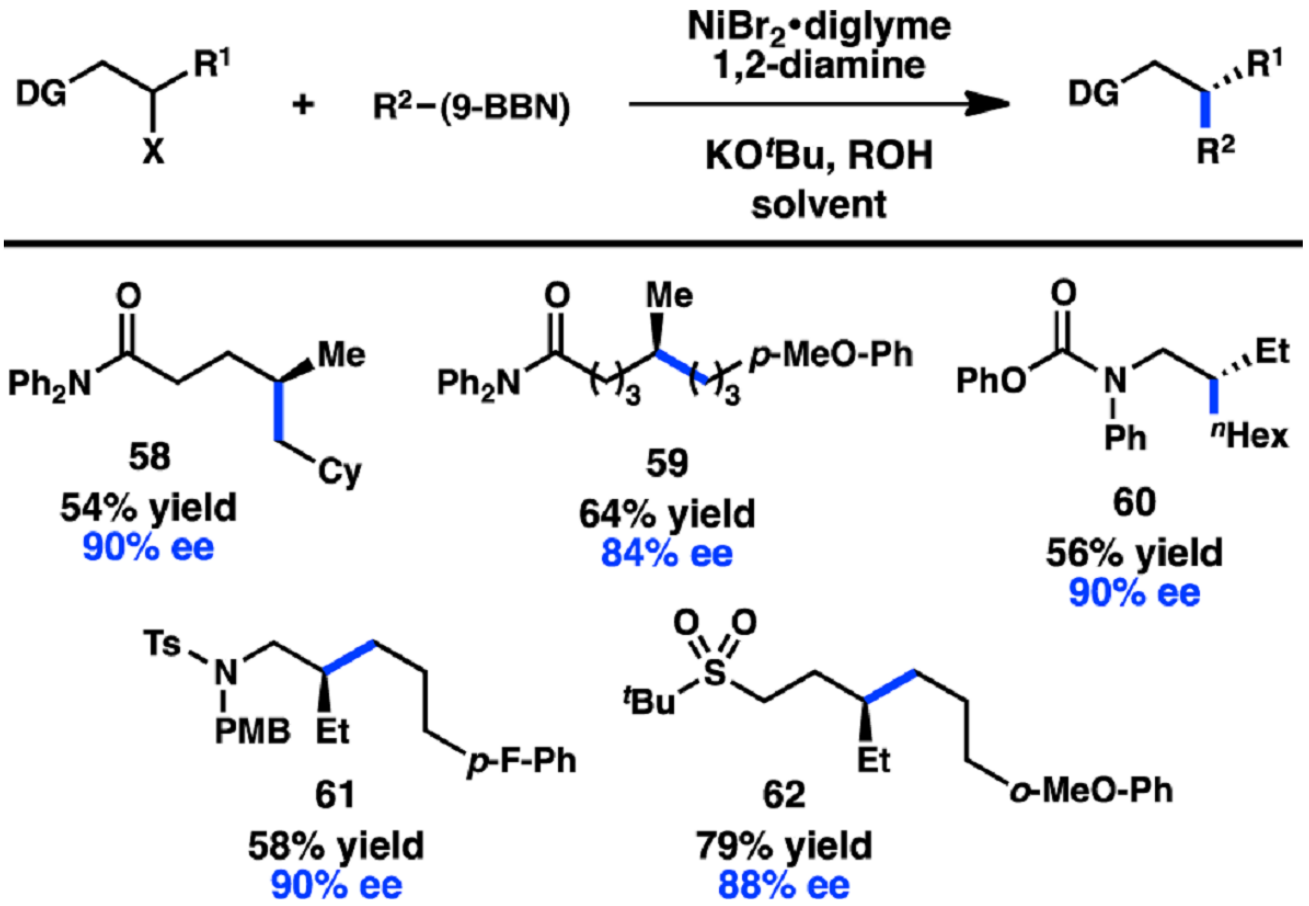
With Organoboron Reagent (Suzuki-Miyaura)

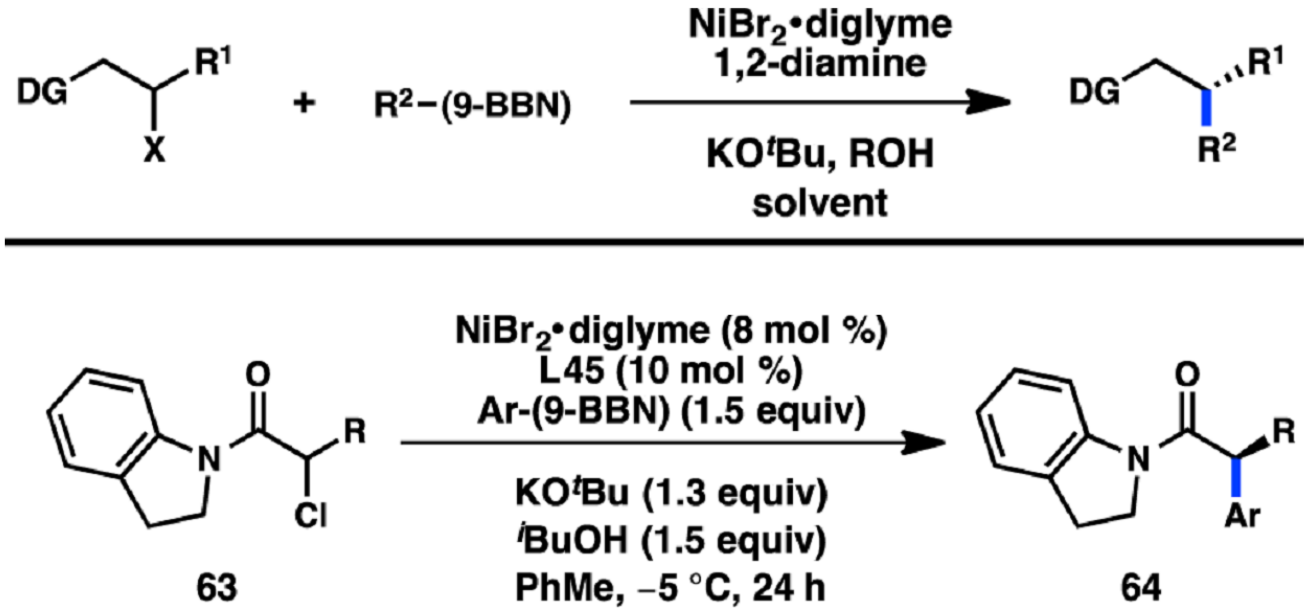
a) Enantioselective alkyl-alkyl Suzuki–Miyaura coupling



Fu, G. C. *et al. J. Am. Chem. Soc*. **2008**, *130*, 6694

Examples of directing groups for enatioconvergent Suzuki-Miyaura coupling





Fu, G. C. *et al. J. Am. Chem. Soc*. **2010**, *132*, 11027

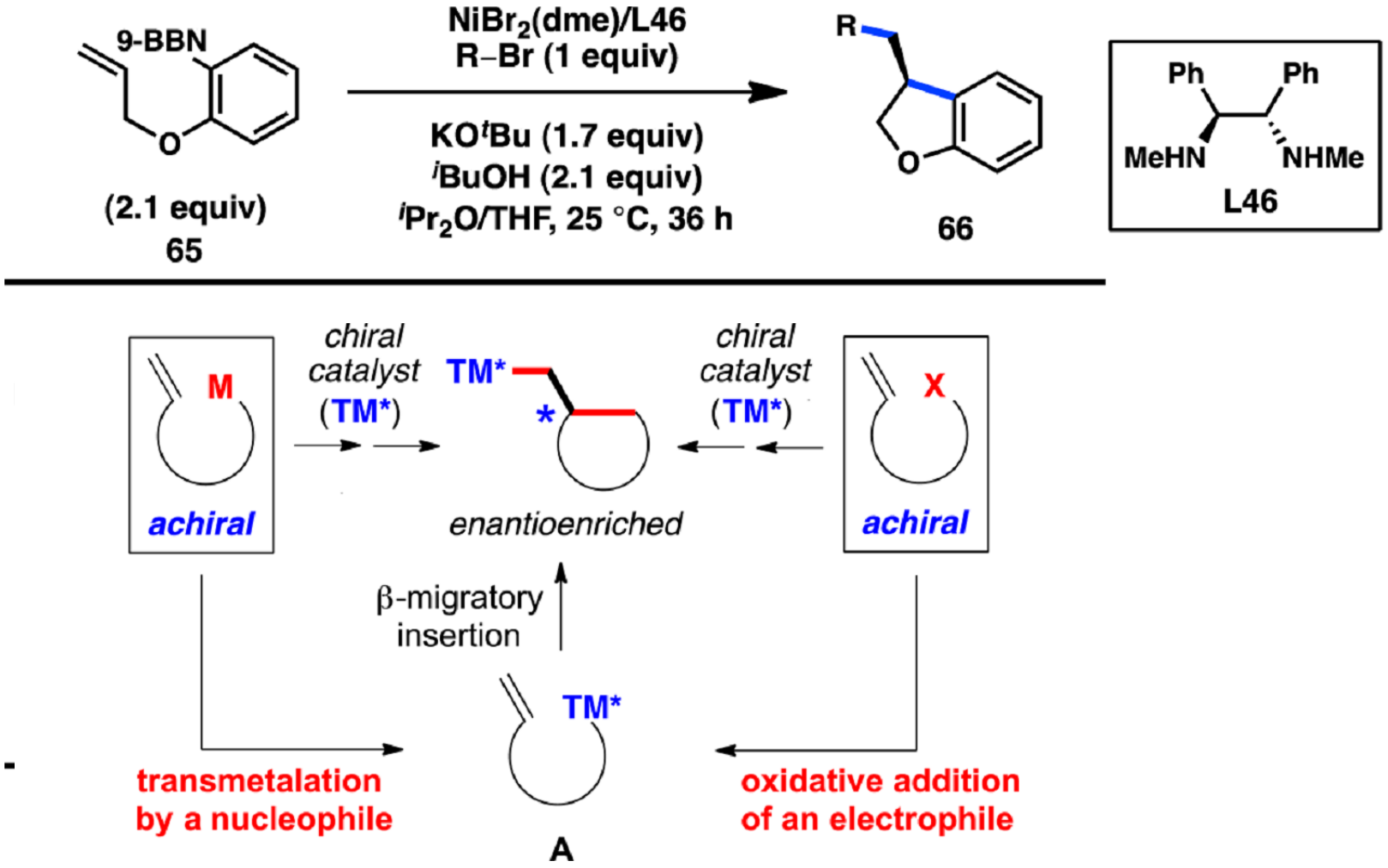
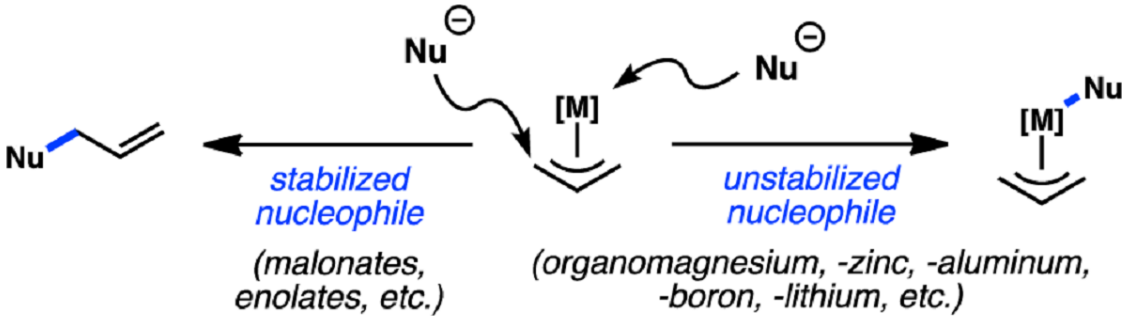


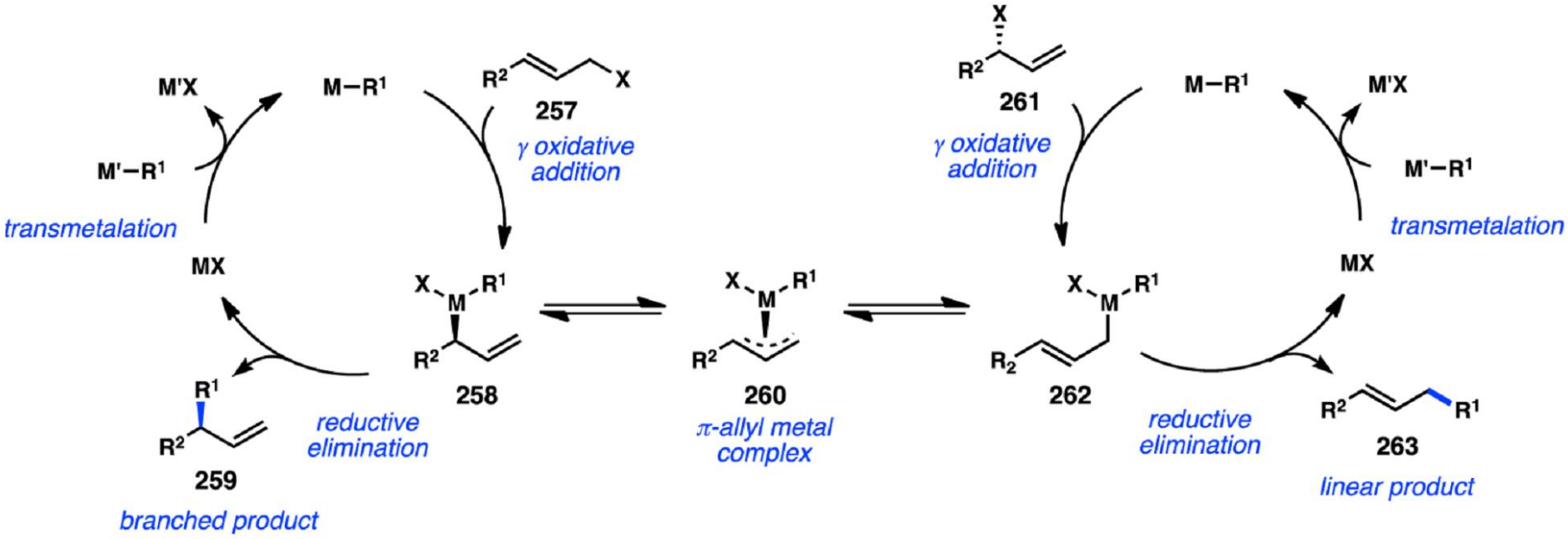
Figure 2. Complementary approaches to generating a precursor (A) for catalytic enantioselective cyclizations.

Fu, G. C. *et al. J. Am. Chem. Soc*. **2014**, *136*, 3788

Transition-Metal-Catalyzed Enantiocontrolled Allylic Substitution



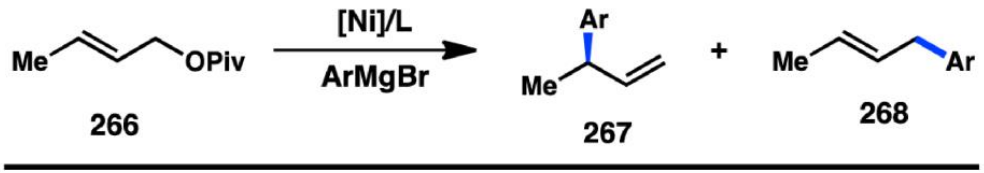
General principles of allylic substitution with hard nucleophiles

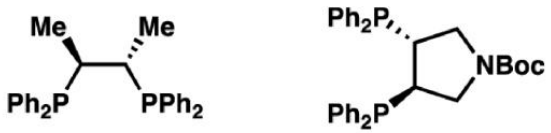


Enantioselective Allylic Substitution Reactions

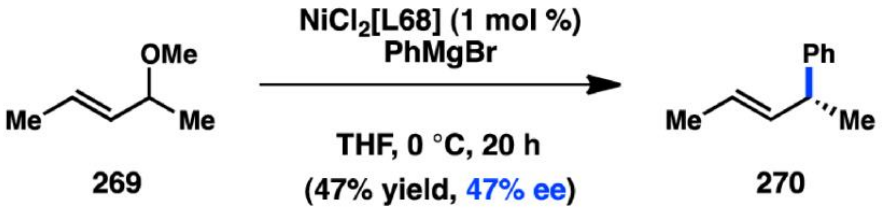
Organomagnesium Reagents

a) Coupling of acyclic electrophiles

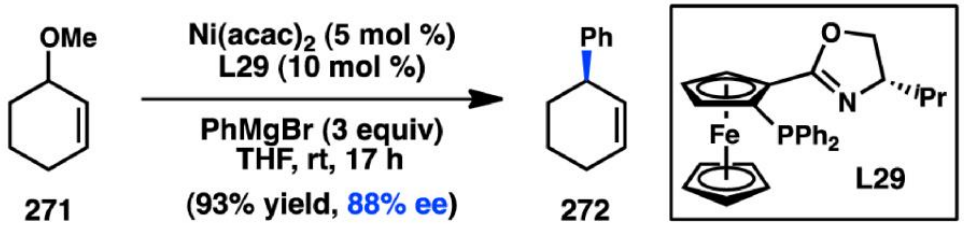




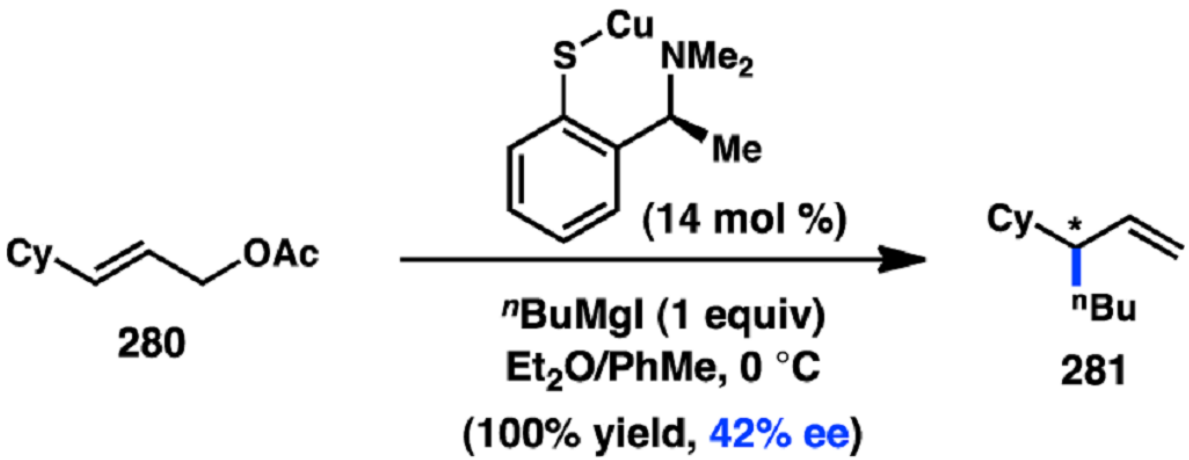
b) Coupling of symmetrical electrophiles



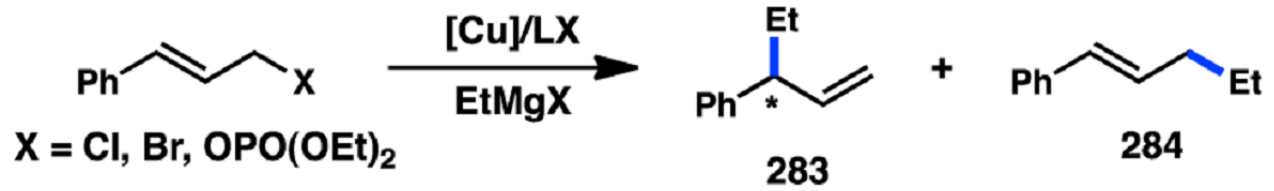
c) Coupling of cyclic electrophiles



Seminal Example of Cu-Catalyzed Asymmetric Allylic Substitution with Alkyl



Van Koten, G. *et al. Tetrahedron Lett*. **1995**, *36*, 3059

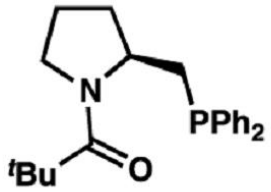


X = Cl, Br, $OPO(OEt)_2$

282

283

284

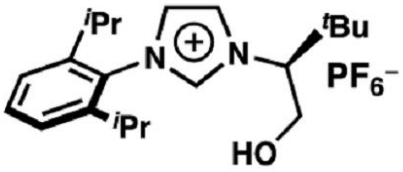


L72

95% yield

62:38 *b:l*

91% ee



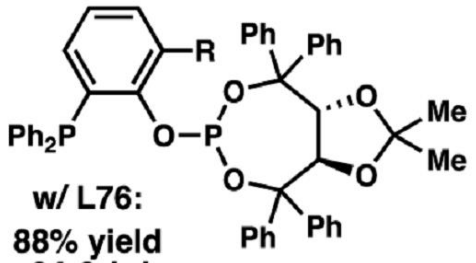
L74

>99% conv.

>98:2 *b:l*

90% ee

(Mauduit, 2013)



w/ L76:

88% yield

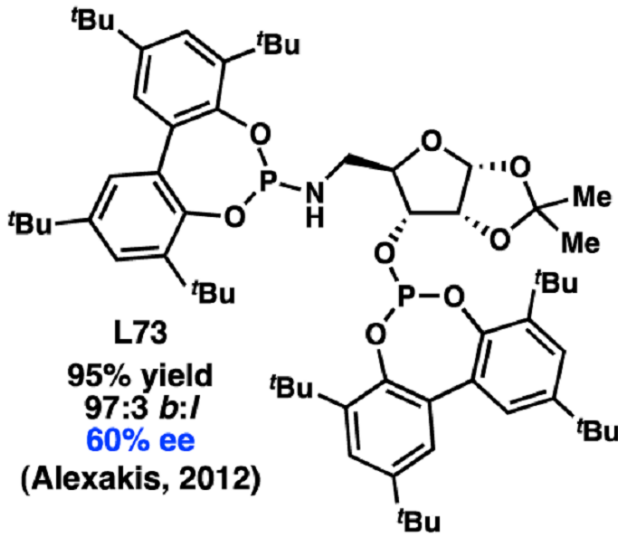
94:6 *b:l*

85% ee

(Schmalz, 2010)

L76 R = ^{i}Pr

L77 R = Ph



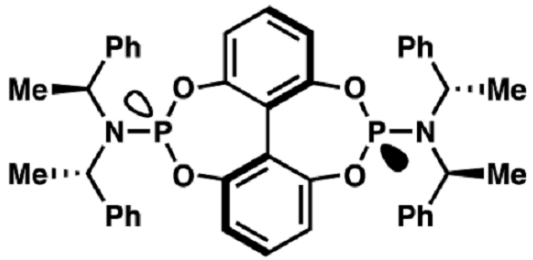
L73

95% yield

97:3 *b:l*

60% ee

(Alexakis, 2012)



L75

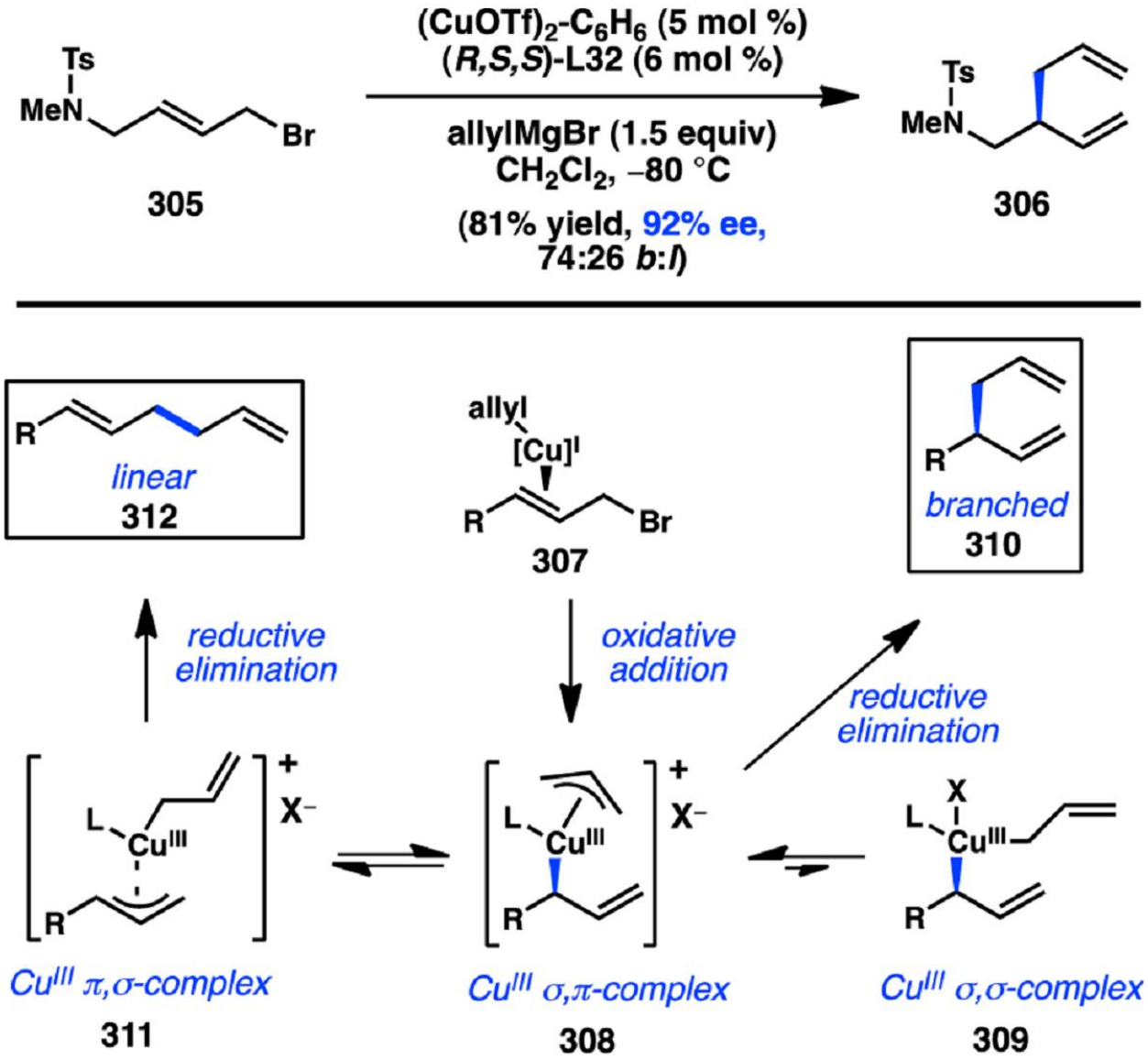
100% conv.

92:8 *b:l*

88% ee

(Zhang, 2010)

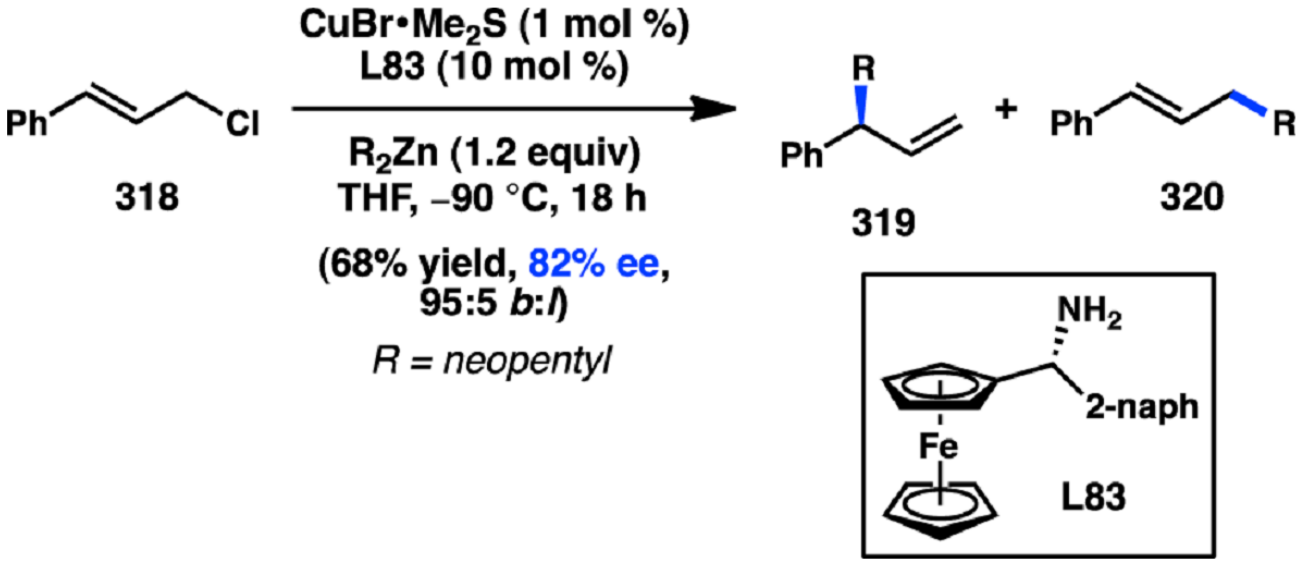
Cu-catalyzed allyl−allyl coupling



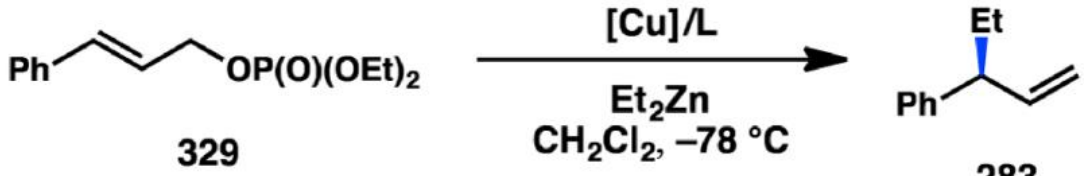
Feringa, B. L. *et al. J. Am. Chem. Soc.* **2013**,*135*, 2140

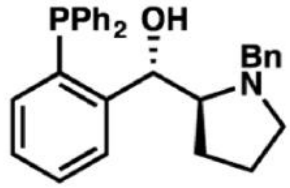
Organozinc Reagents

Seminal Enantioselective Cu-Catalyzed Substitution of Allylic Chlorides

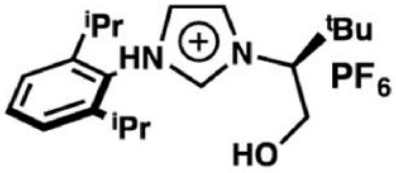


Knochel, P. *et al. Angew. Chem. Int. Ed*. **1999**, *38*, 379

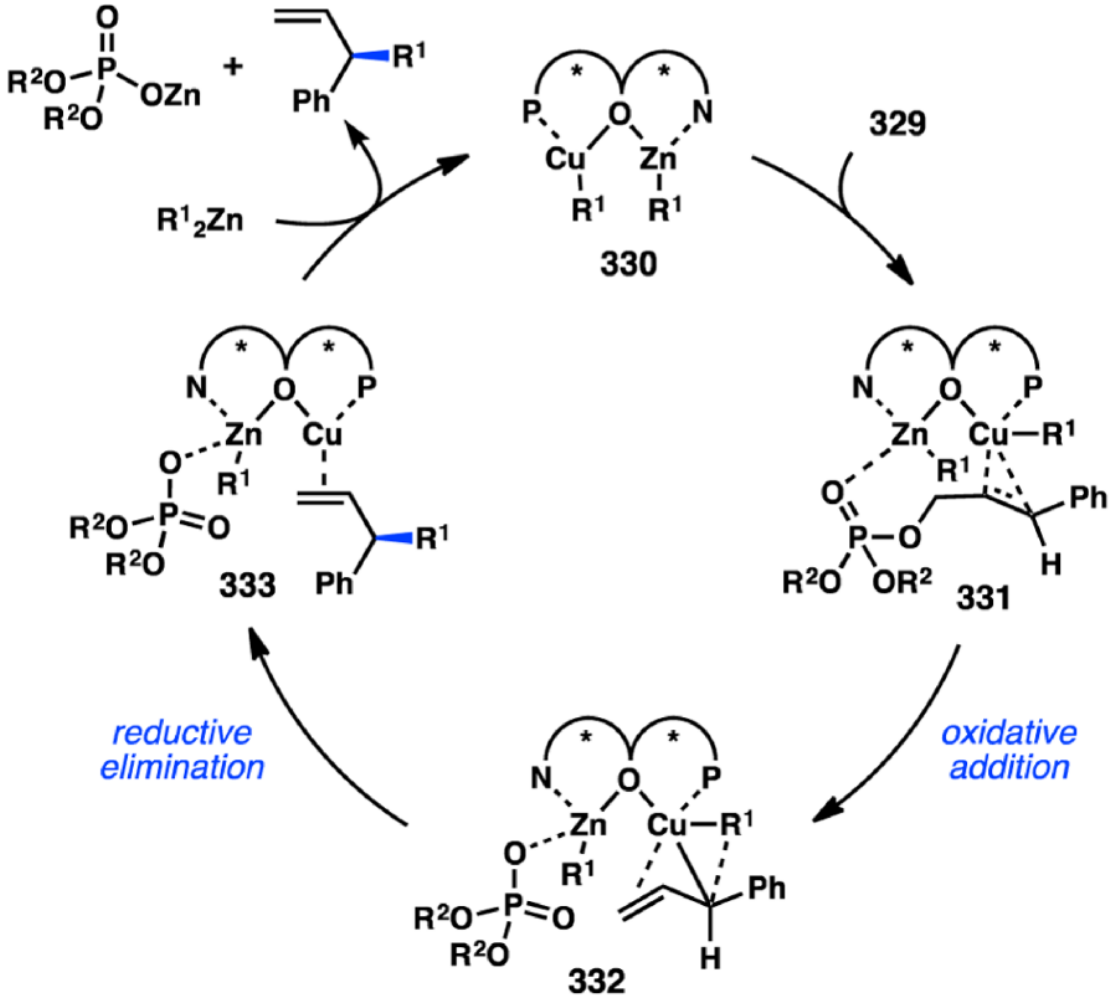




L87
53% yield
96% ee
(Nakamura, 2009)

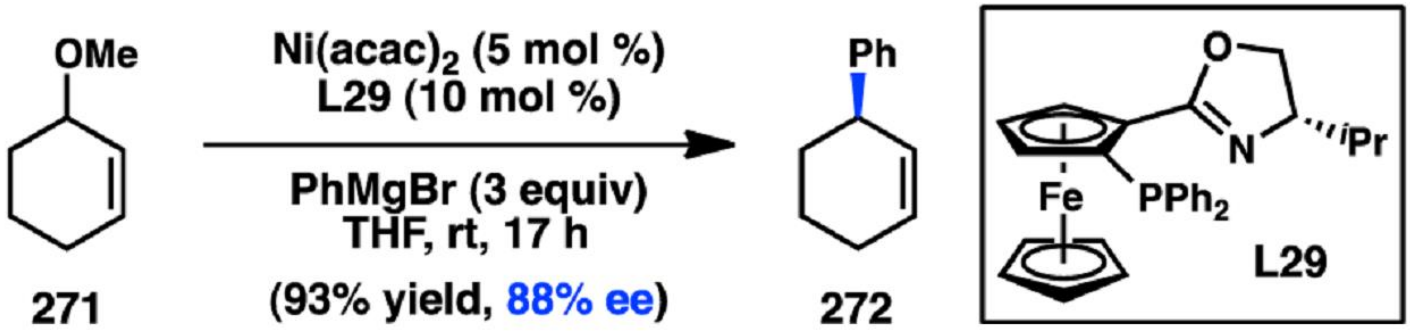


L88
90% yield
96% ee
(Mauduit, 2010)



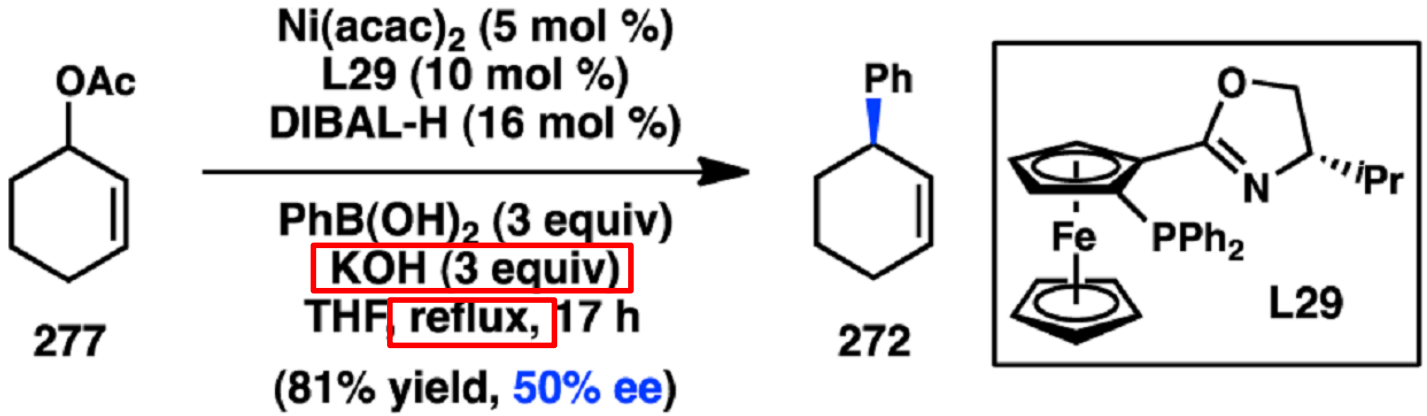
Organoboron Reagents

With Organomagnesium Reagents



271 272

With Organoboron Reagents



277 272

Organoboron Reagents

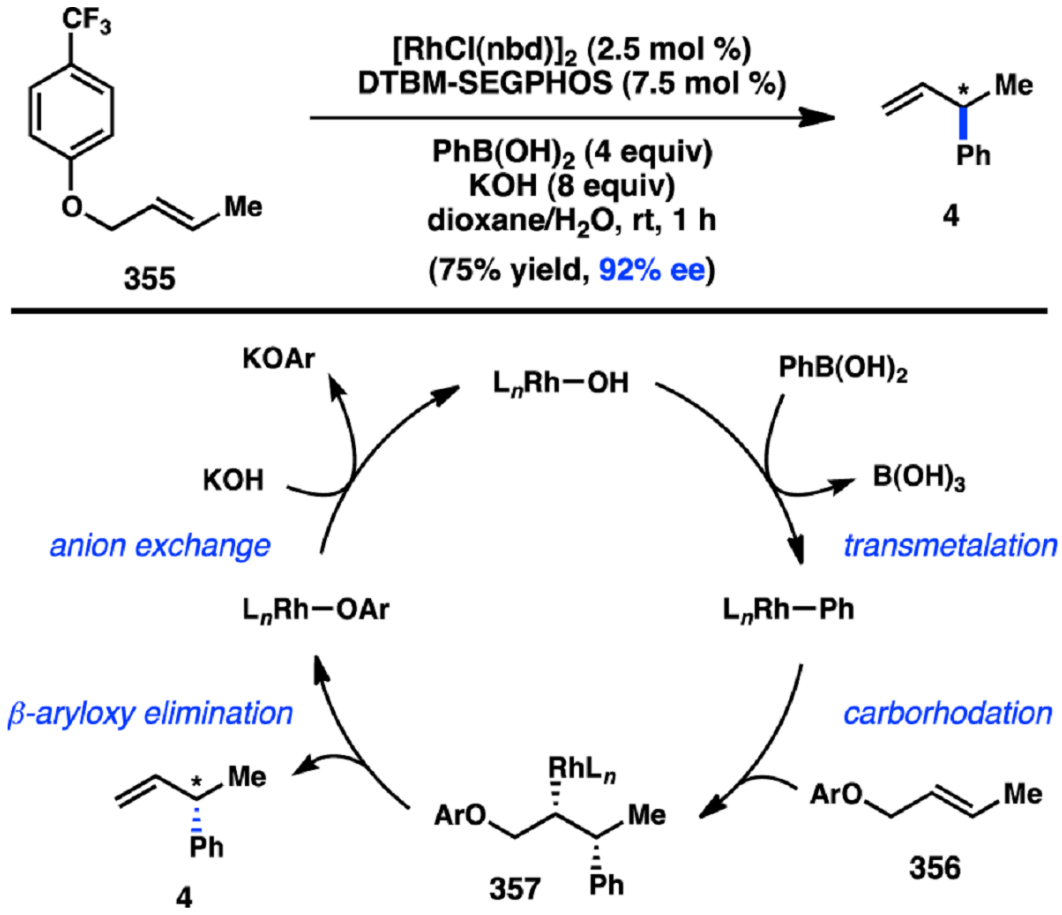
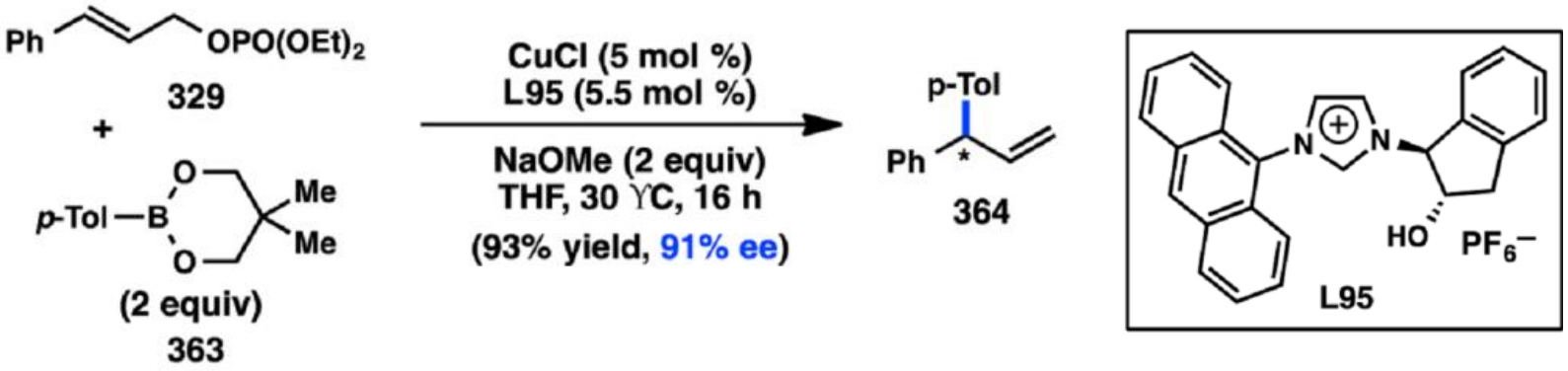
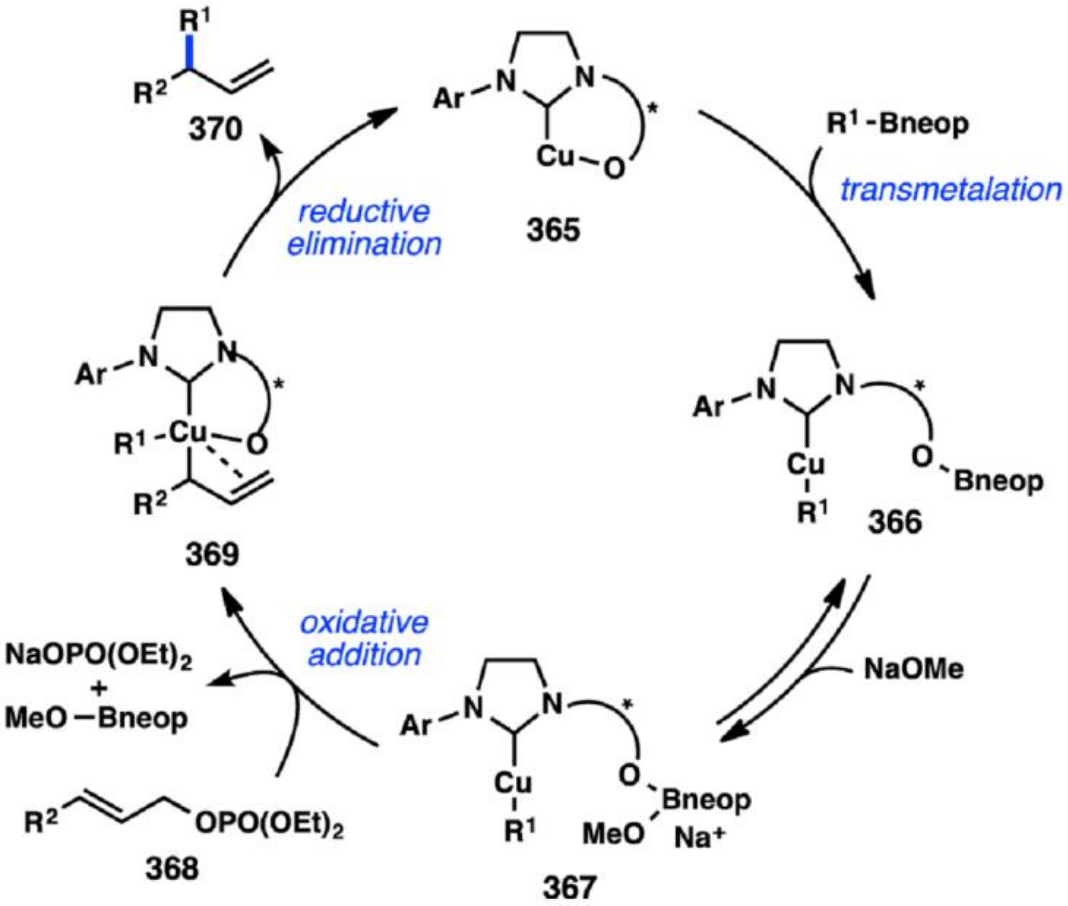


Figure 73. Allylic substitution of allyl aryl ethers.

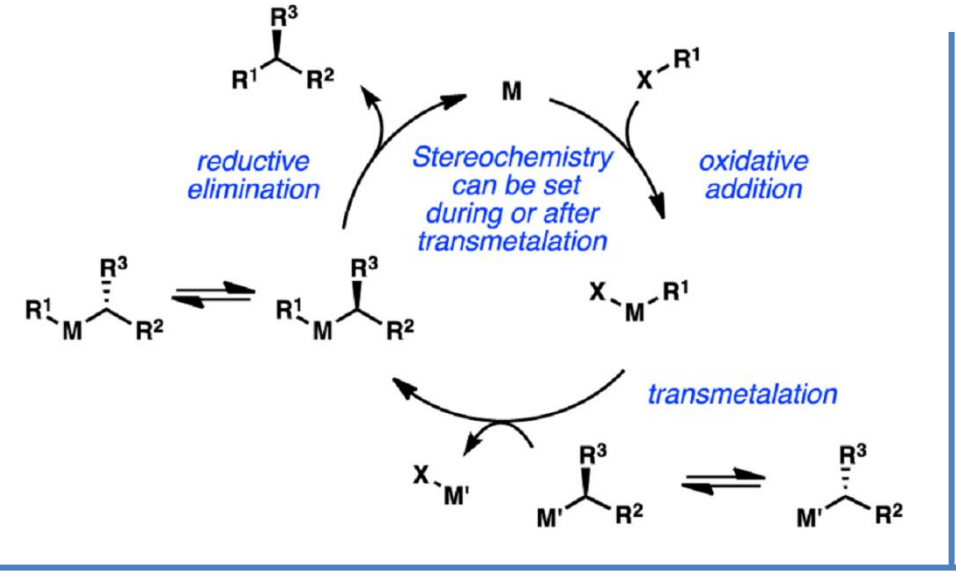
Oi, S. *et al. Org. Lett*. **2012**, *14*, 4502

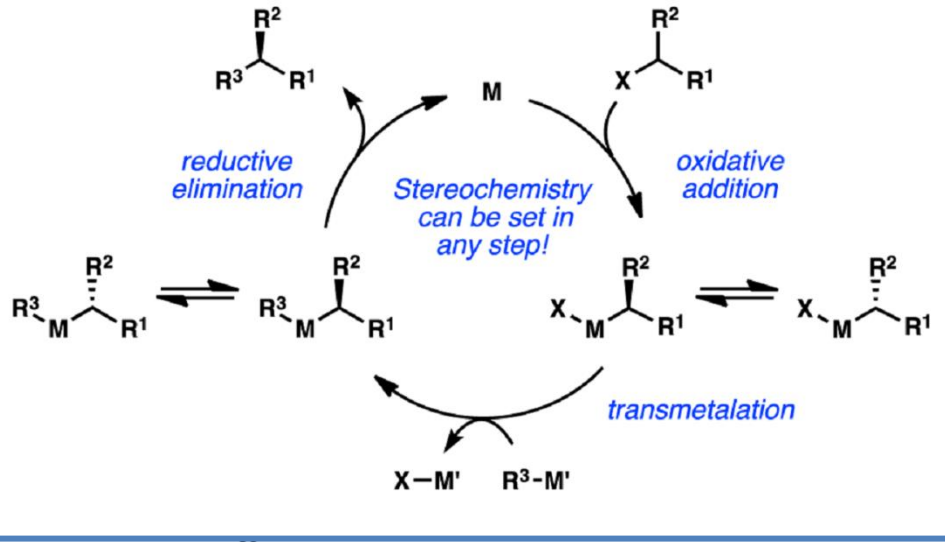


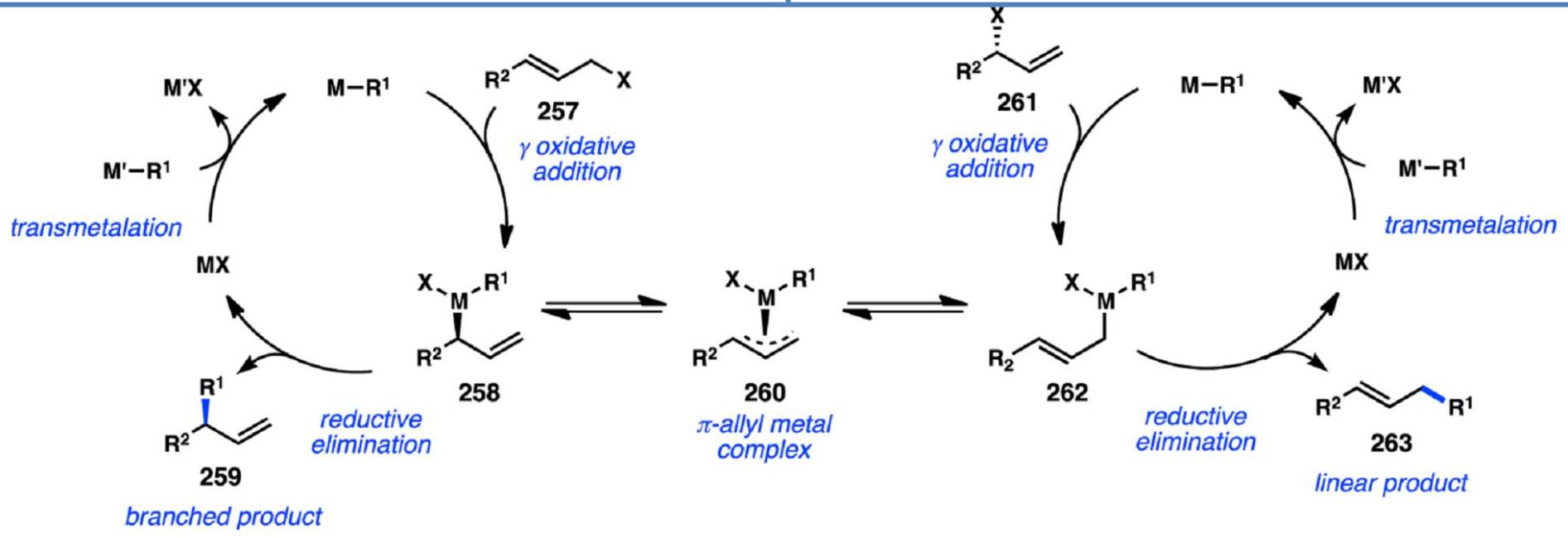


Hayashi, T. *et al. Angew. Chem. Int. Ed*. **2011**, *50*, 8656

Summmary


reductive elimination
Stereochemistry can be set during or after transmetalation
oxidative addition
transmetalation


reductive elimination
Stereochemistry can be set in any step!
oxidative addition
transmetalation


M'X
M–R1
M'–R1
transmetalation
MX
257
γ oxidative addition
258
259
branched product
reductive elimination
260
π-allyl metal complex
261
γ oxidative addition
262
263
linear product
reductive elimination

1）the analogous asymmetric cross-coupling reactions of tert-alkyl partners represent a largely undeveloped area

2） provide entry to molecules with all-carbon quaternary centers

3）few ligands have been shown to support a broad substrate scope with high selectivity

Thank you !

Sarash E. Reisman *et al. Chem. Rev*. ASAP