

# ***Iron-Catalyzed Cross-Coupling Reactions***

Literature seminar #1

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2019/1/17

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1. Introduction

2. Developement of iron-catalyzed cross-coupling reactions

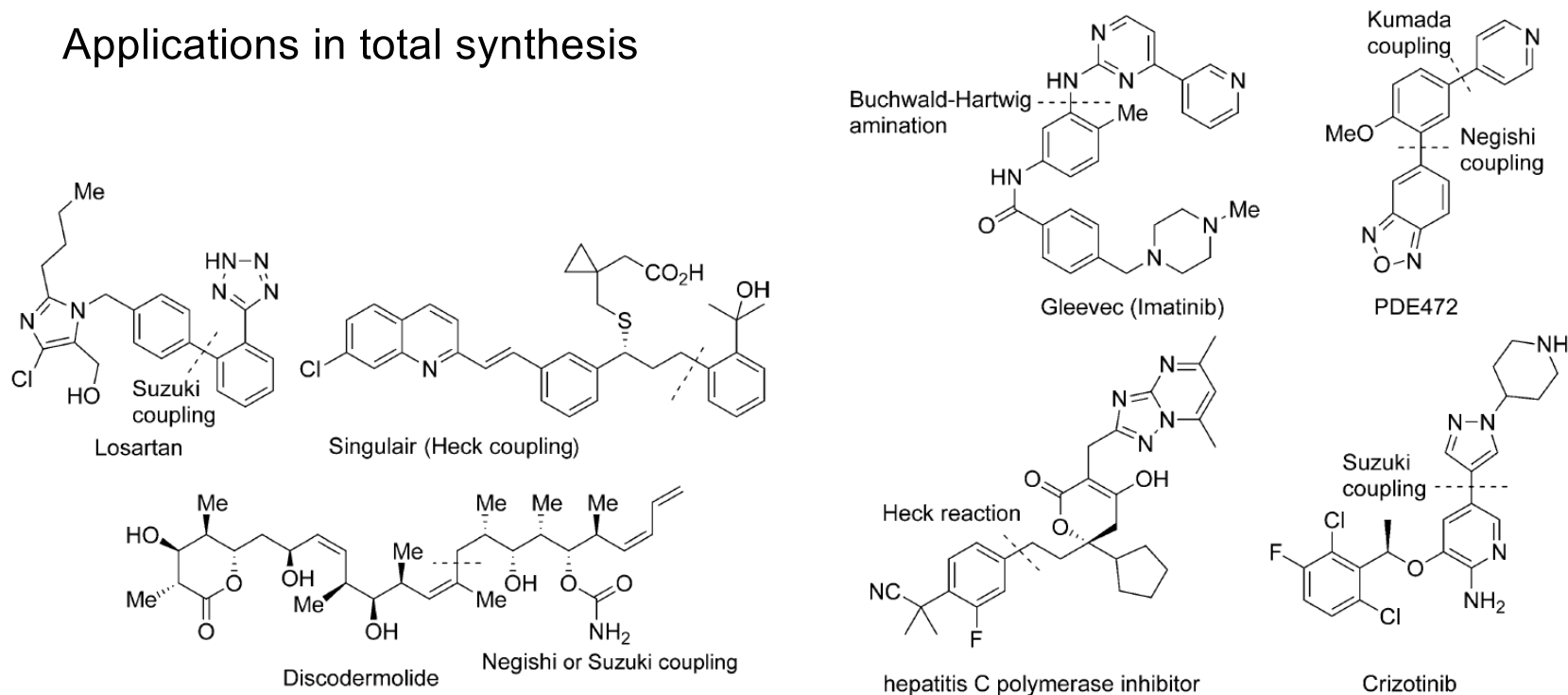
- Kumada-Tamao-Corriu coupling
- Negishi coupling
- Suzuki-Myaura coupling

3. Iron-catalyzed enantioselective cross-coupling reaction

# Introduction

- **Metal-catalyzed cross-coupling reaction is important C-C bond forming process in organic synthesis.**

## Applications in total synthesis



- In particular, Pd- and Ni-catalyzed cross-coupling are well developed.

# Introduction

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- **Benefits of iron catalysis**

Pd Ni



Fe

- ease of handling and development

- inexpensive
- less toxic
- earth-abundant
- environmentally friendly

Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170.

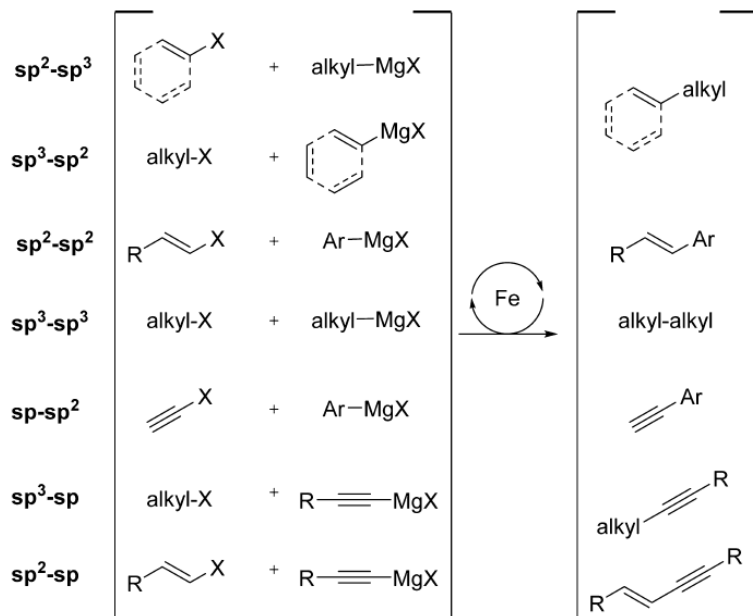
Cassani, C.; Bergonzini, G.; Wallentin, C.-J. *ACS Catal.* **2016**, *6*, 1640.

Sears, J. D.; Neate, P. G. N.; Neidig, M. L. *J. Am. Chem. Soc.* **2018**, *140*, 11872.

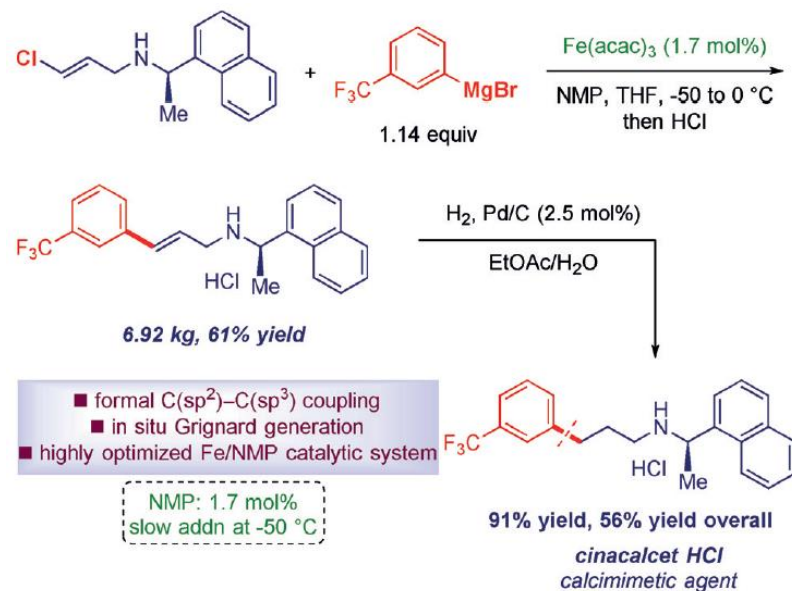
# Introduction

- Iron-catalyzed cross-coupling has been rapidly developing since the late 90s.

## Examples



## Application



Cassani, C.; Bergonzini, G.; Wallentin, C.-J. *ACS Catal.* **2016**, *6*, 1640.

Piontek, A.; Bisz, E.; Szostak, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 11116.

Tewari, N.; Maheshwari, N.; Medhane, R.; Nizar, H.; Prasad, M. *Org. Process Res. Dev.* **2012**, *16*, 1566.

# Introduction

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- **Challenges of mechanistic studies of iron-catalyzed reactions**
  1. Broad range of plausible reaction mechanisms  
(Both one- and two-electron pathway are possible.)
  2. Experimental challenges associated with characterizing paramagnetic iron complexes  
(many oxidation states and spin states)
- However, lack of mechanistic insight limits mechanism-driven development of iron-catalyzed reactions.

Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170.

Cassani, C.; Bergonzini, G.; Wallentin, C.-J. *ACS Catal.* **2016**, *6*, 1640.

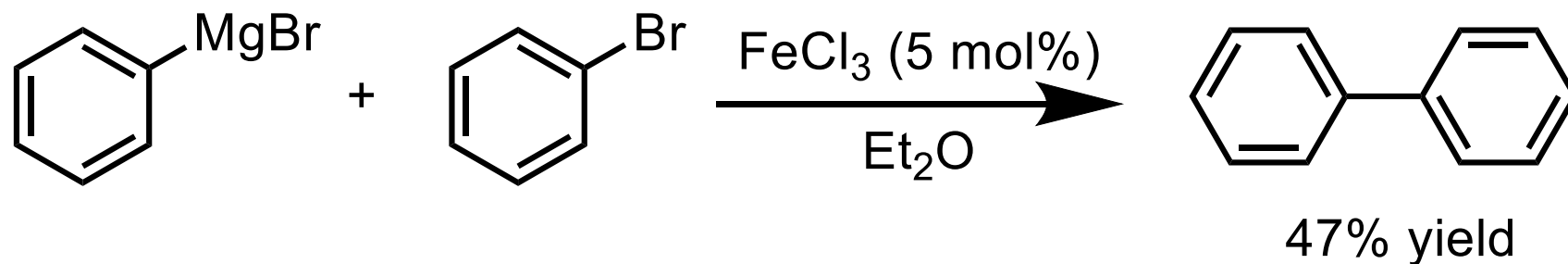
Sears, J. D.; Neate, P. G. N.; Neidig, M. L. *J. Am. Chem. Soc.* **2018**, *140*, 11872.

## ***2. Developement of iron-catalyzed cross-coupling reactions***

### ***Kumada-Tamao-Corriu coupling***

# Kumada-Tamao-Corriu Coupling

- First reported iron-catalyzed cross-coupling by Kharasch in 1941

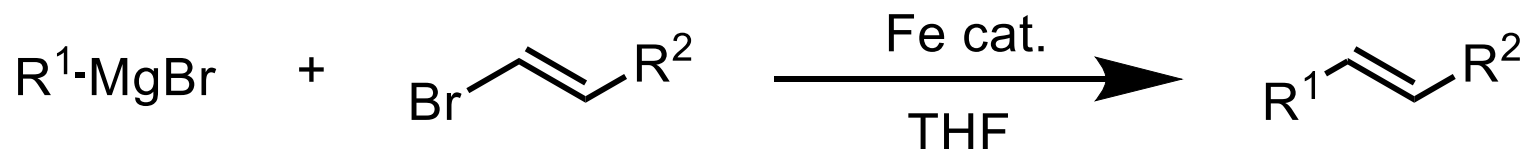


- An aryl Grignard reagent reacted with an organic halide in the presence of small amount of  $\text{FeCl}_3$ .



# Kumada-Tamao-Corriu Coupling

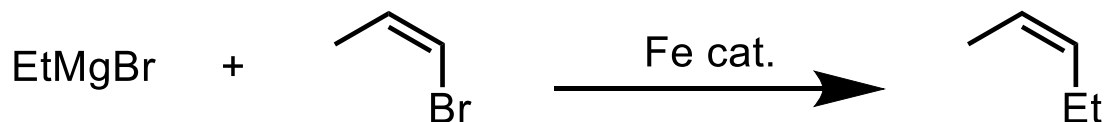
- Kochi's pioneering works in 1970s



alkyl

- alkenyl Grignard reagent × alkenyl halide

Ph-

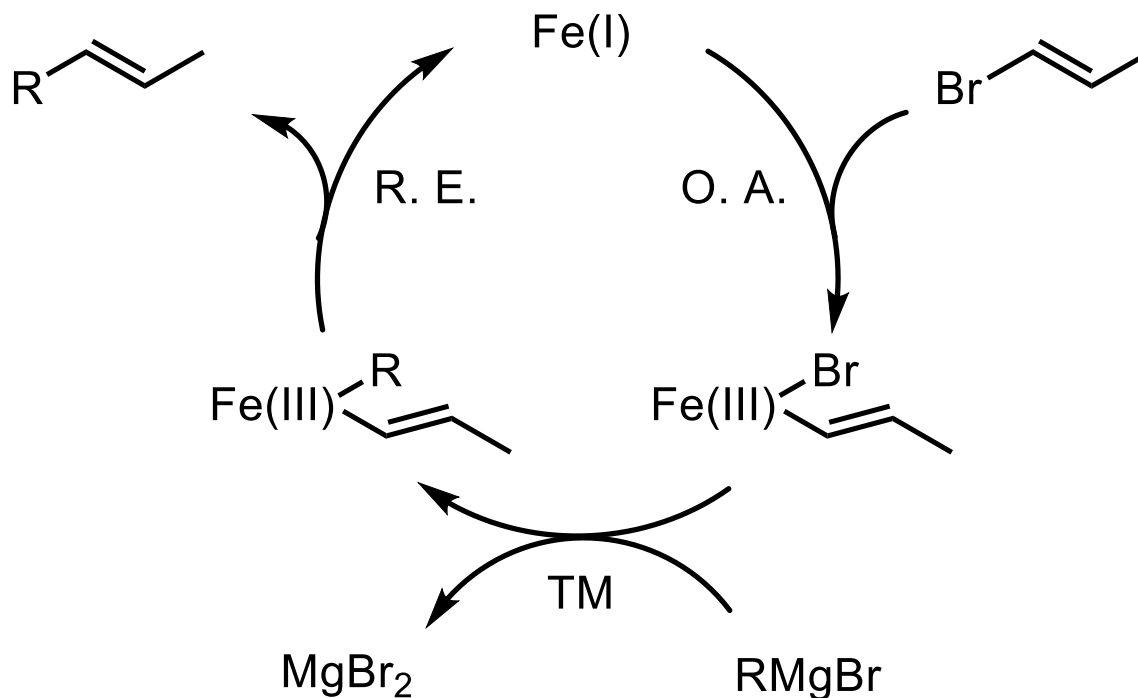


- The cross-coupling product was formed stereospecifically.
- A trans-isomer reacted 15 times faster than a cis-isomer.

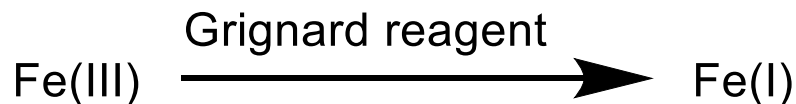
Tamura, M.; Kochi, J. K. *Synthesis* **1971**, 1971, 303.  
Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, 93, 1487.  
Neumann, S. M.; Kochi, J. K. *J. Org. Chem.*, **1975**, 40, 599.  
Smith, R. S.; Kochi, J. K. *J. Org. Chem.*, **1976**, 41, 502.

# Kumada-Tamao-Corriu Coupling

- Kochi proposed Fe(I)/Fe(III) catalyst cycle.



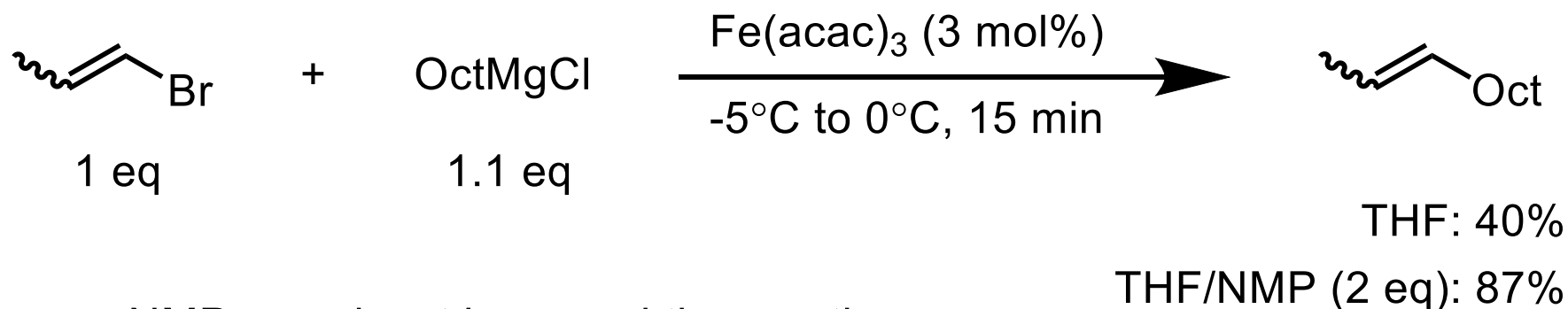
- Formation of Fe(I) species



Smith, R. S.; Kochi, J. K. *J. Org. Chem.*, **1976**, *41*, 502.

# Kumada-Tamao-Corriu Coupling

- Cahiez demonstrated practical iron-catalyzed cross-coupling reaction.



- NMP co-solvent improved the reaction.
- addressing limitations of Kochi's protocol
  - requirement of excess electrophile (3-5 eq) and moderate yield
- utilizing broader substrate scopes
  - alkyl Grignard reagent × alkenyl halide
    - aryl (-I, -Br, -Cl)
    - + functional group tolerance (ketone, ester, nitrile)

Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1998, 1199.

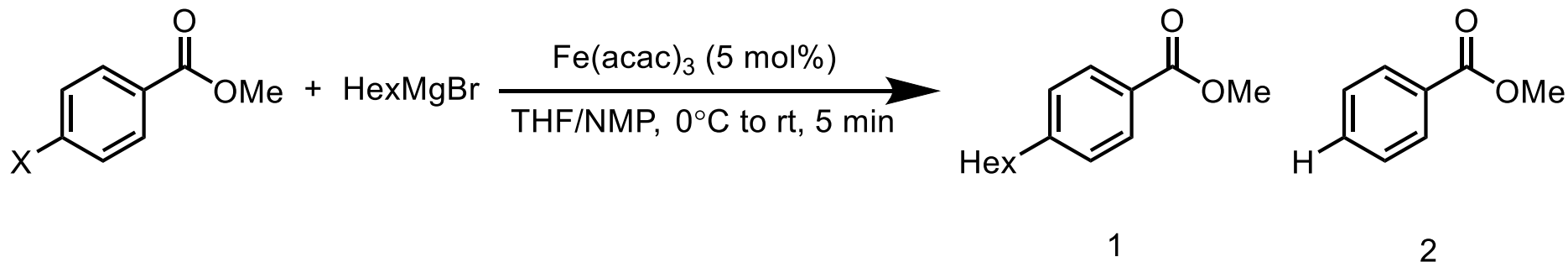
Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 2001 (12), 1901.

Cahiez, G.; Marquais, S. *Tetrahedron Lett.* **1996**, 37, 1773.

Cahiez, G.; Marquais, S. *Pure & Appl. Chem.*, **1996**, 68, 53.

# Kumada-Tamao-Corriu Coupling

- Fürstner reported iron-catalyzed cross-coupling with aryl electrophiles.



Entry	X	yield (%)	
		1	2
1	I	27	46
2	Br	38	50
3	Cl	>95	-
4	OTf	>95	-
5	OTs	>95	-

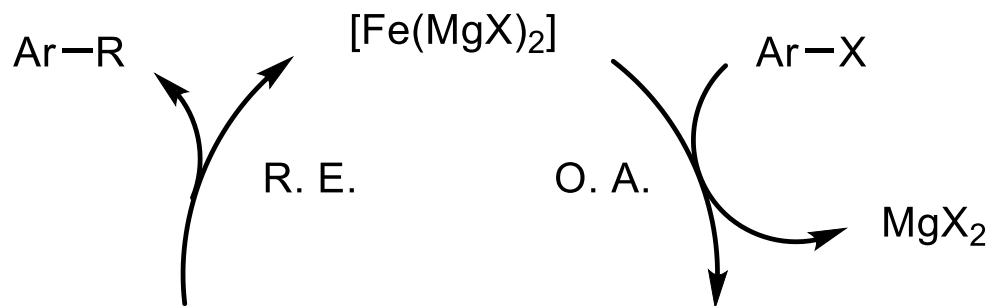
- Ar-Cl, -OTf, -OTs are more effective substrates than Ar-I, -Br.

Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609.

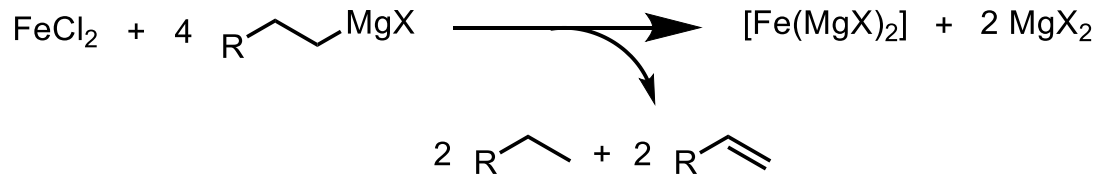
Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

# Kumada-Tamao-Corriu Coupling

- Fürstner proposed Fe(-II)/Fe(0) cycle.



- Formation of Fe(-II) species



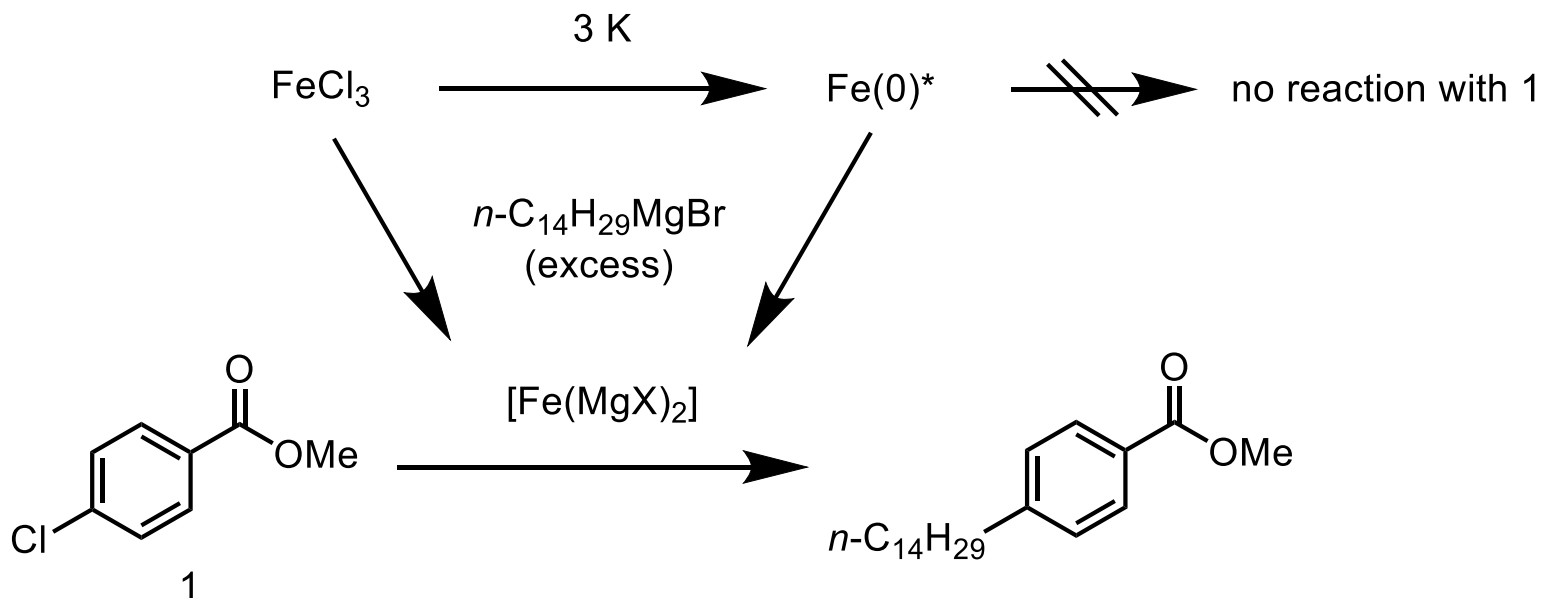
Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609.

Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.

# Kumada-Tamao-Corriu Coupling

- **Mechanistic study**



- $\text{Fe}(0)^*$  does not insert the C-Cl bond, but the cross-coupling occurs in the presence of an excess of Grignard reagent.
- They also demonstrated that  $\text{Fe}(\text{-II})$  complexes can act as precatalyst.

Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.

# Kumada-Tamao-Corriu Coupling

- Norrby suggested Fe(I)/Fe(III) cycle by computational studies.



**Table 3.** Free energies ( $\text{kJ mol}^{-1}$ ) for postulated reductive elimination steps.

''Fe''	No. sol <sup>[a]</sup>	Ox. State <sup>[b]</sup>	$\Delta G$	$\Delta G^\ddagger$
FeMg	3	-II	195	-
FeMgCl	3	-I	94	-
Fe	2	0	30	191
FeCl	2	+I	-181	10

[a] Number of explicit solvent molecules ( $\text{Me}_2\text{O}$ ) used in the calculation.

[b] Oxidation state of Fe after reductive elimination.

- Reductive elimination to form Fe(-II) and Fe(-I) is thermodynamically very unfavorable.
- The energy barrier of reductive elimination to form Fe(0) is prohibitive.

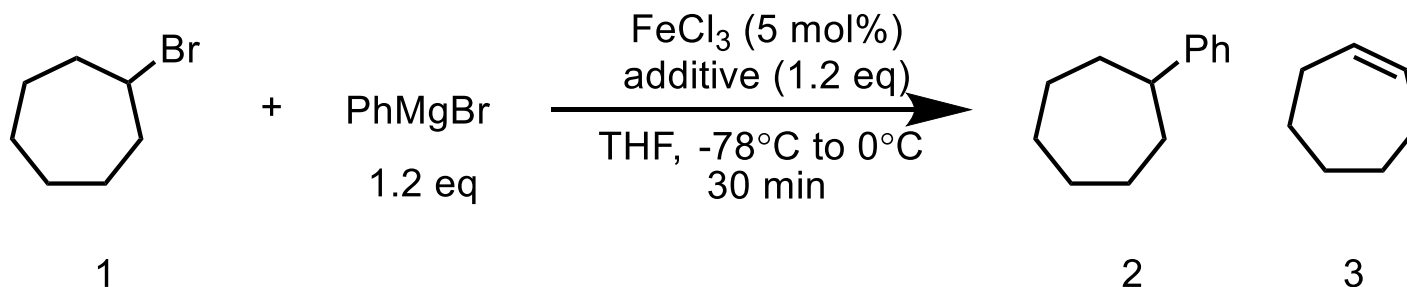
- Low valent Fe species may act as precatalyst, but they cannot be regenerated under reaction conditions.

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- This study also suggests that oxidative addition is rate-determining step.

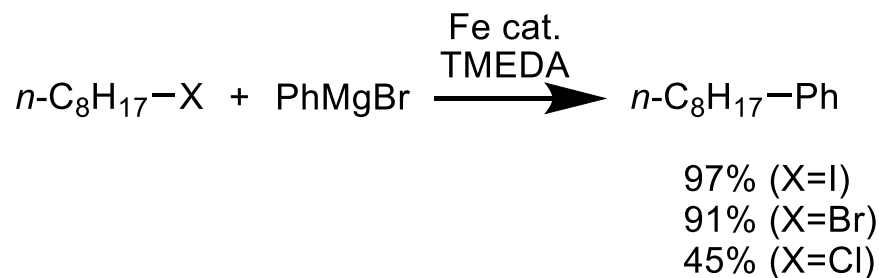
# Kumada-Tamao-Corriu Coupling

- Nakamura, Hayashi, Fürstner, and Bedford reported iron-catalyzed cross-coupling reaction of alkyl halide and aryl Grignard reagent in 2004.

Nakamura's example



entry	additive	yield (%)		
		2	3	1
1	none	5	79	4
2	Et <sub>3</sub> N	3	78	11
3	N-methyl morpholine	8	72	4
4	DABCO	20	2	75
5	NMP	15	3	79
6	TMEDA	71	19	trace



- Addition of TMEDA suppresses  $\beta$ -hydride elimination. reactivity: alkyl iodide > bromide > chloride

Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686.

Nagano, T.; Hayashi, T. *Org. Lett.*, **2004**, *6*, 1297.

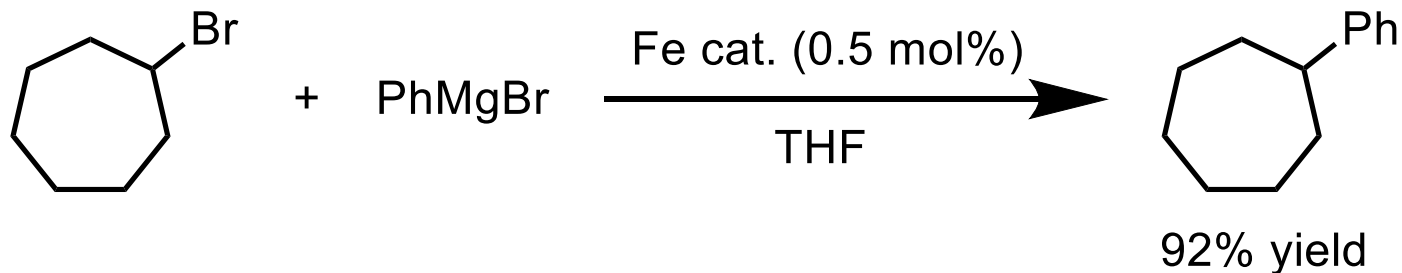
Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955.

Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822.

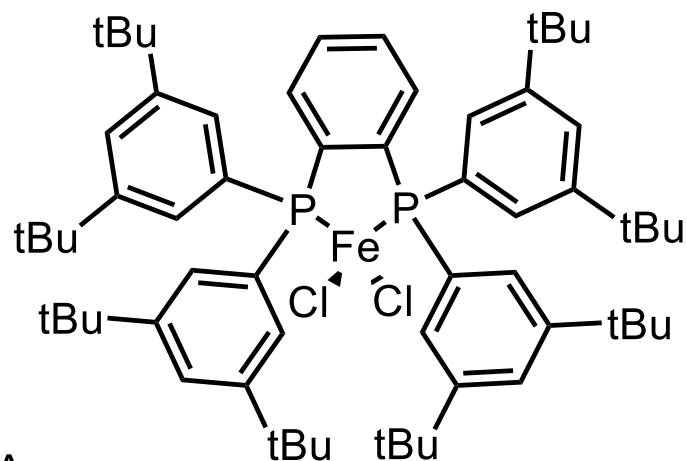


# Kumada-Tamao-Corriu Coupling

- Bisphosphine ligand SciOPP is effective.



Fe cat. :  
[FeCl<sub>2</sub>(3,5-t-Bu<sub>2</sub>-SciOPP)]



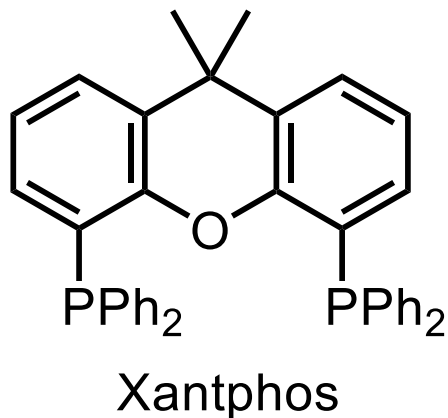
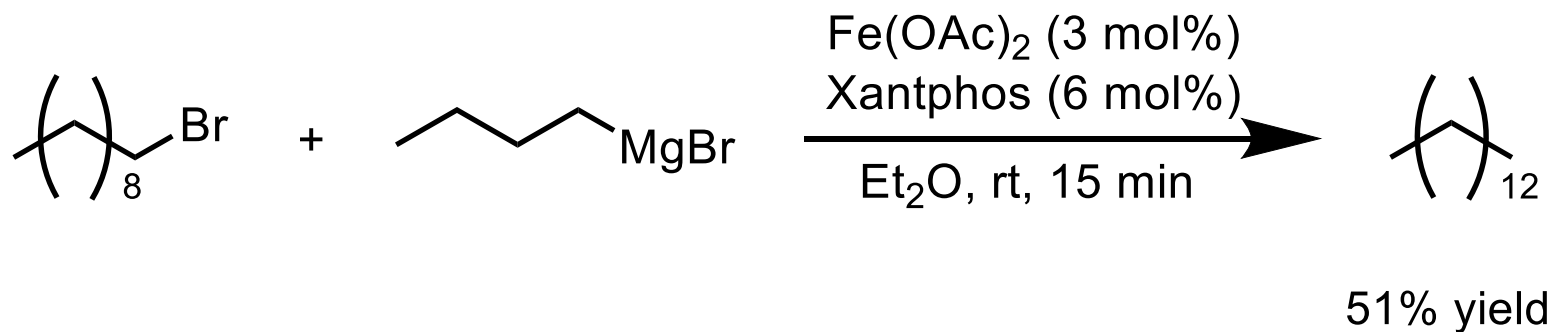
- No need of a large excess of TMEDA

Hatakeyama, T.; Fujiwara, Y.; Okada, Y.; Itoh, T.; Hashimoto, T.; Kawamura, S.; Ogata, K.; Takaya, H.; Nakamura, M. *Chem. Lett.* **2011**, *40*, 1030.



# Kumada-Tamao-Corriu Coupling

- Chai reported iron-catalyzed  $sp^3$ - $sp^3$  Kumada coupling.

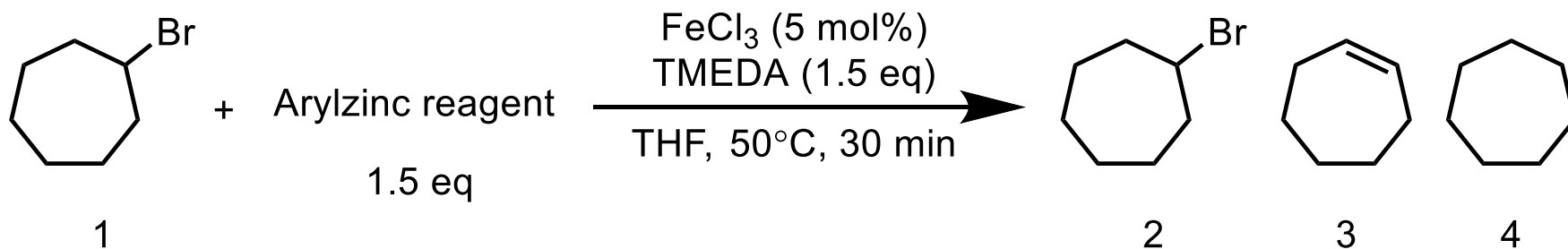


- Alkyl radical intermediates were suggested by radical clock experiments

# ***Negishi coupling***

# Negishi Coupling

- In 2005 Nakamura developed iron-catalyzed Negishi coupling.



Entry	Arylzinc reagent	yield (%)			
		2	3	4	1
1	$\text{ZnCl}_2/2\text{PhMgBr}$	96	3	trace	0
2	$\text{ZnCl}_2/\text{PhMgBr}$	0	trace	trace	>95%
3	$\text{PhZnBr}$ (Mg free)	0	trace	trace	>95%
4 <sup>a</sup>	$\text{ZnCl}_2/2\text{PhLi}$	0	trace	trace	>95%
5 <sup>b</sup>	$\text{ZnCl}_2/\text{PhMgBr}/\text{TMSCH}_2\text{MgCl}$	95	4	trace	0

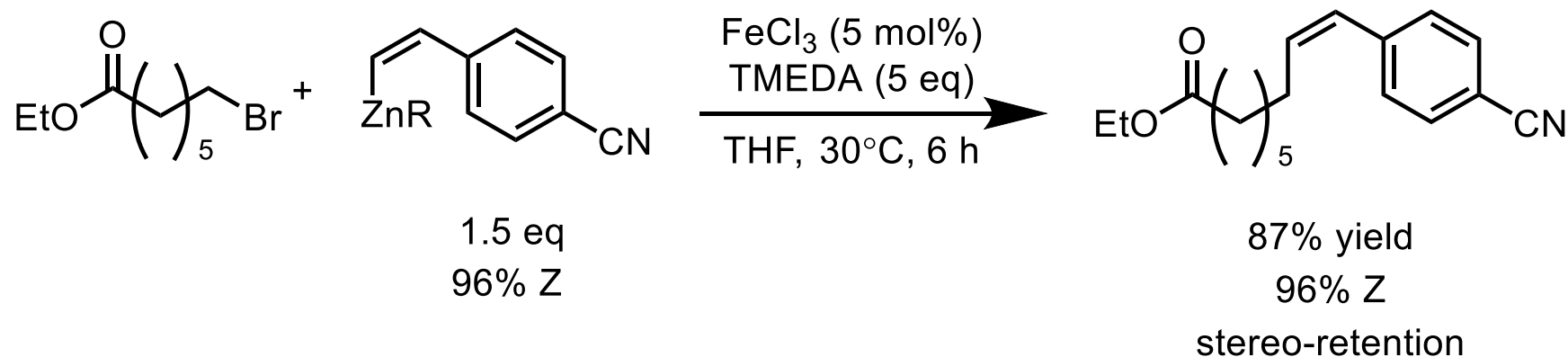
solvent. a:THF/ $\text{Bu}_2\text{O}$ =2/1, b:THF/ $\text{Et}_2\text{O}/\text{Bu}_2\text{O}$ =2/2/1

- A Mg salt is required.
- A diaryl zinc reagent is required, but dummy ligand is effective.

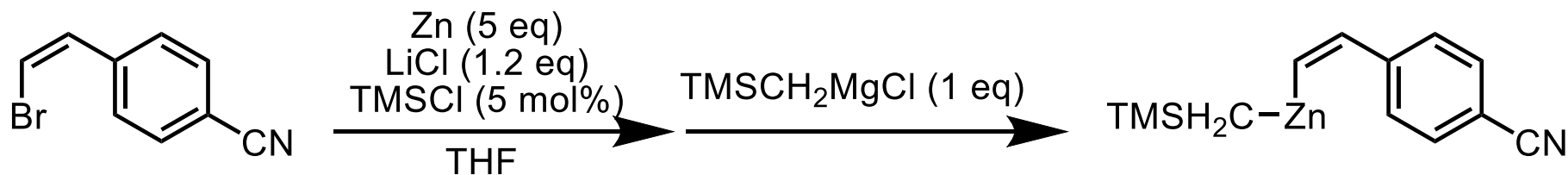
- Radical intermediates were suggested.

# Negishi Coupling

- Nakamura expanded nucleophile scopes into alkenylzinc reagents.

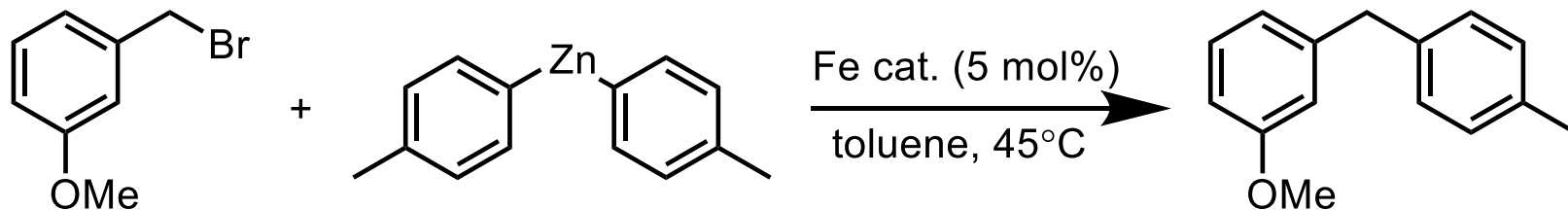


- Preparation of alkenylzinc reagent



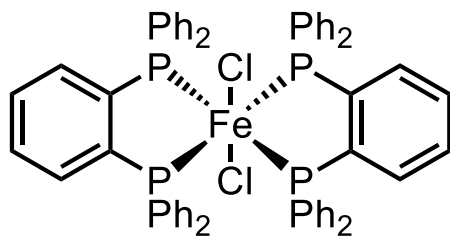
# Negishi Coupling

- Bedford demonstrated diphosphine ligands are effective.



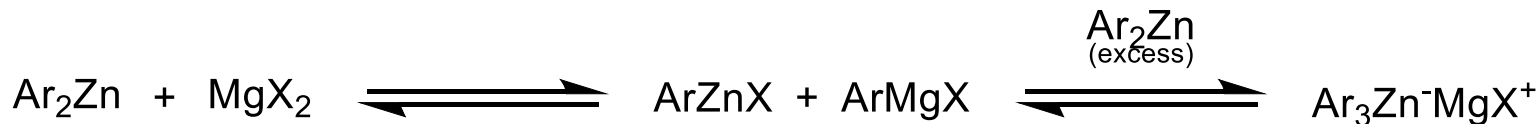
94% yield

Fe cat.:



- A Mg salt is also required.

- The possible role of MgX<sub>2</sub> is explained by generation of zincate complexes.

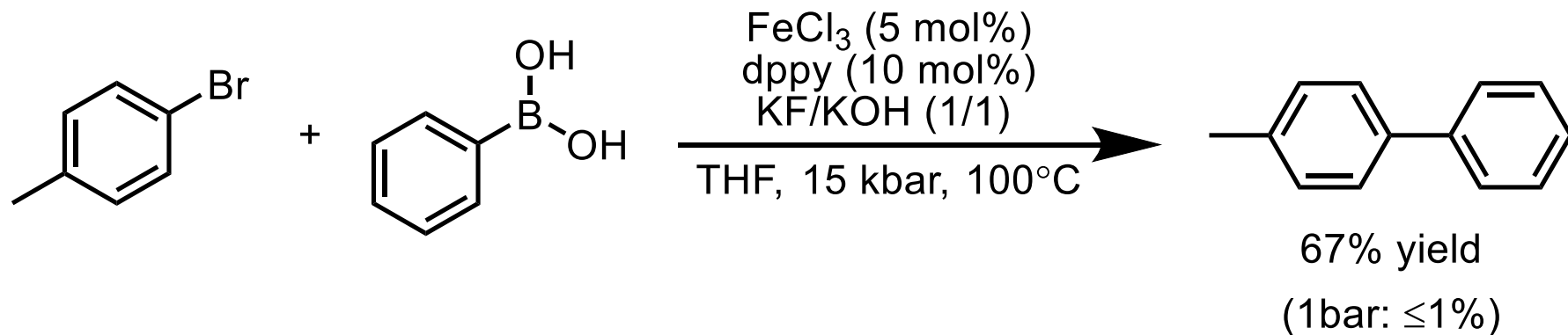


# ***Suzuki-Myaura coupling***



# Suzuki-Miyaura Coupling

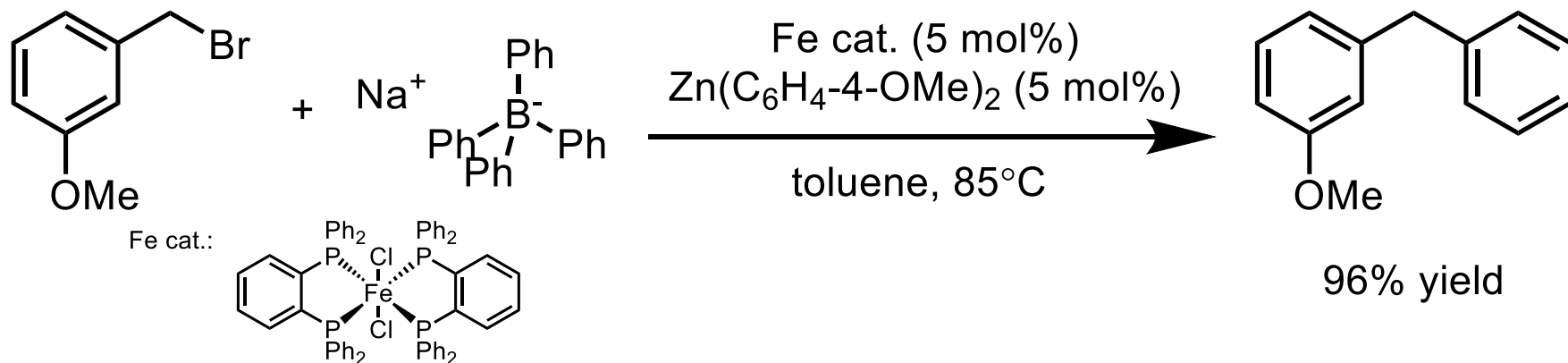
- First iron-catalyzed Suzuki-Miyaura coupling was achieved under elevated pressure.



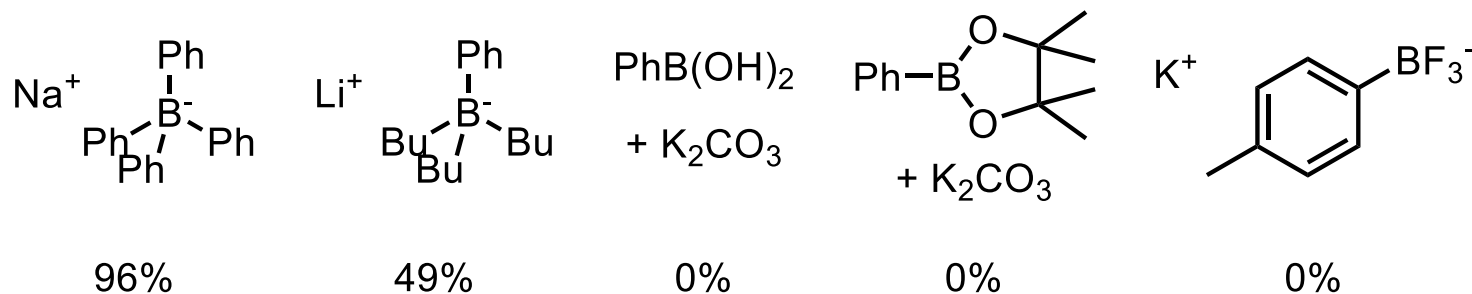
- The primary influence of pressure may be acceleration of reduction to form low valent iron species.

# Suzuki-Miyaura Coupling

- Bedford achieved iron-catalyzed Suzuki coupling under ambient pressure by Fe-Zn co-catalytic system.

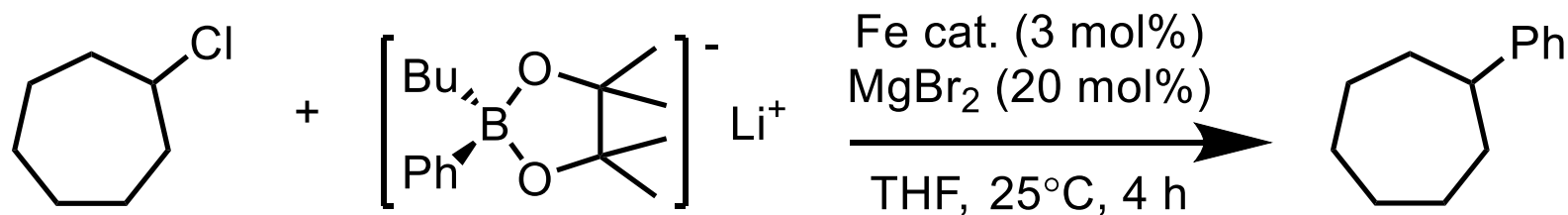


- However, this system utilizes very narrow nucleophile scopes.

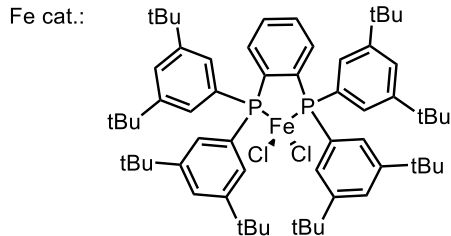


# Suzuki-Miyaura Coupling

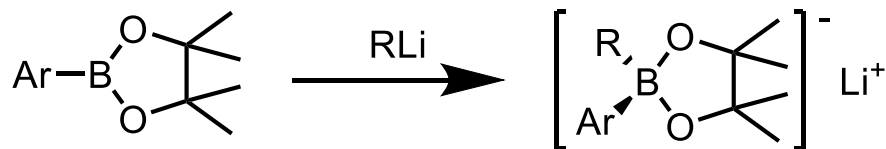
- Nakamura developed iron-catalyzed Suzuki coupling by an iron-diphosphine complex and a Mg salt.



93% yield



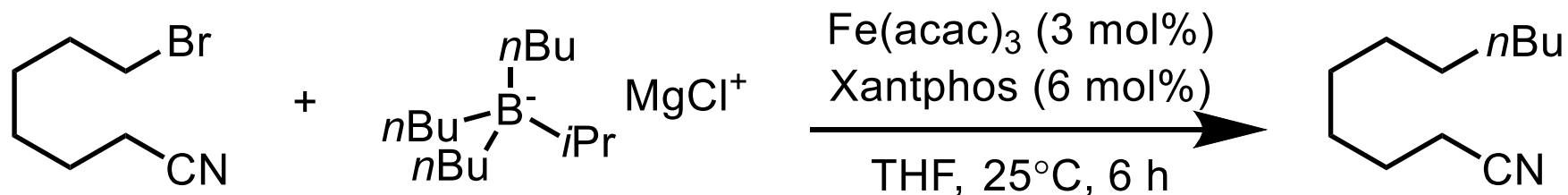
- *In situ* preparation of organoboronates



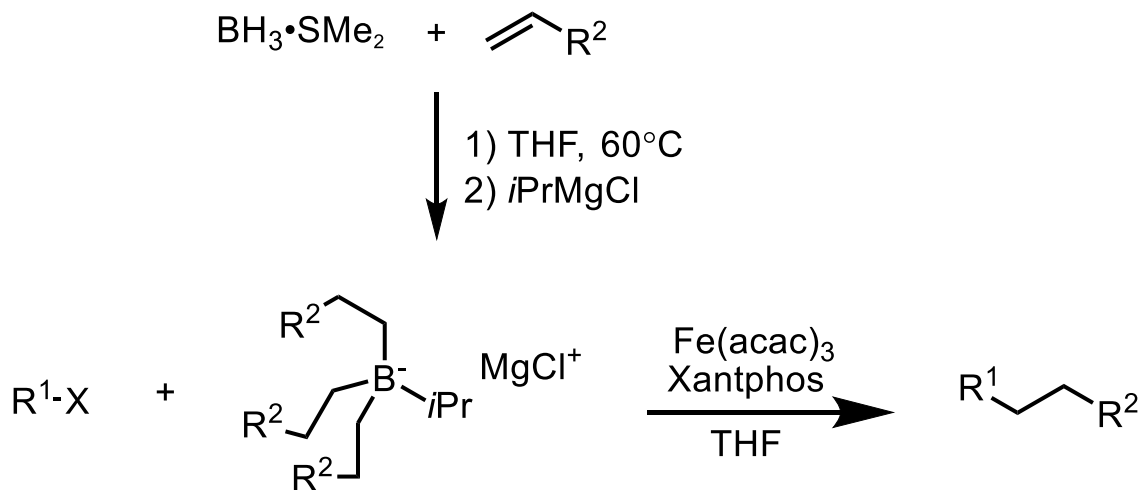
- Broader substrate scopes (alkyl-X × arylboronic acid pinacol ester)
- A Mg salt may accelerate the transmetalation between the boronate and the iron catalyst.

# Suzuki-Miyaura Coupling

- Nakamura expanded this system to alkyl-alkyl Suzuki coupling.



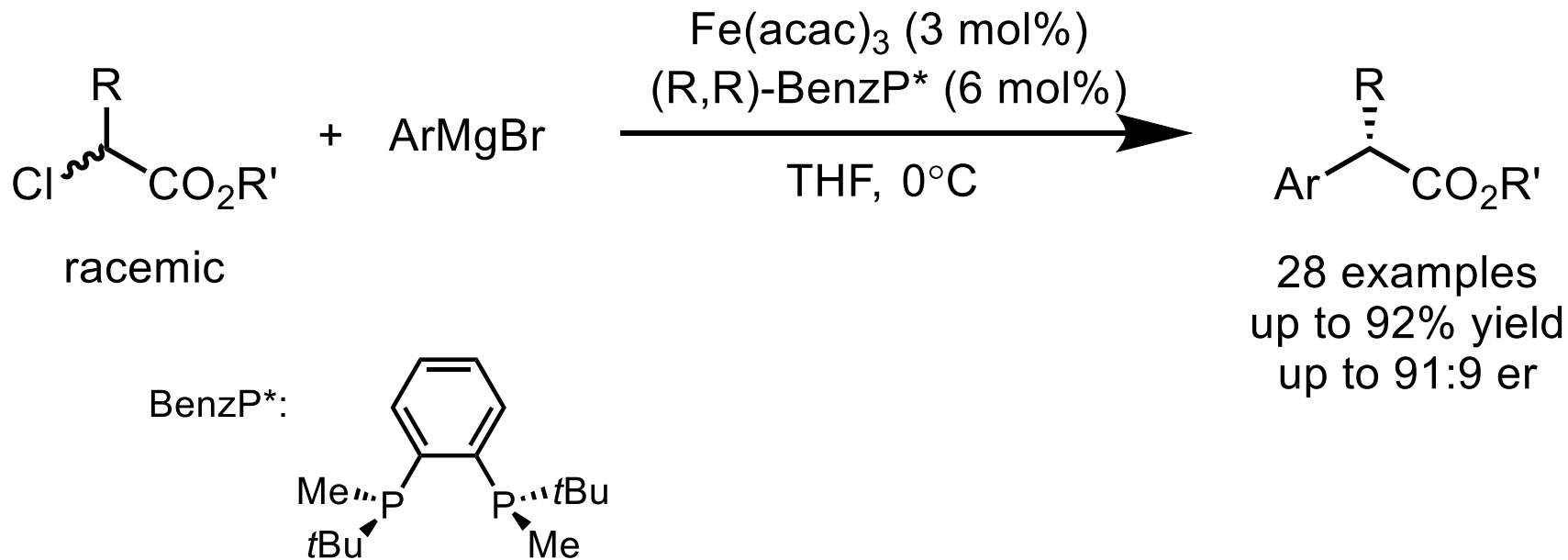
- *In situ* preparation from olefine



### ***3. Iron-catalyzed enantioselective cross-coupling reaction***

# Enantioselective Coupling

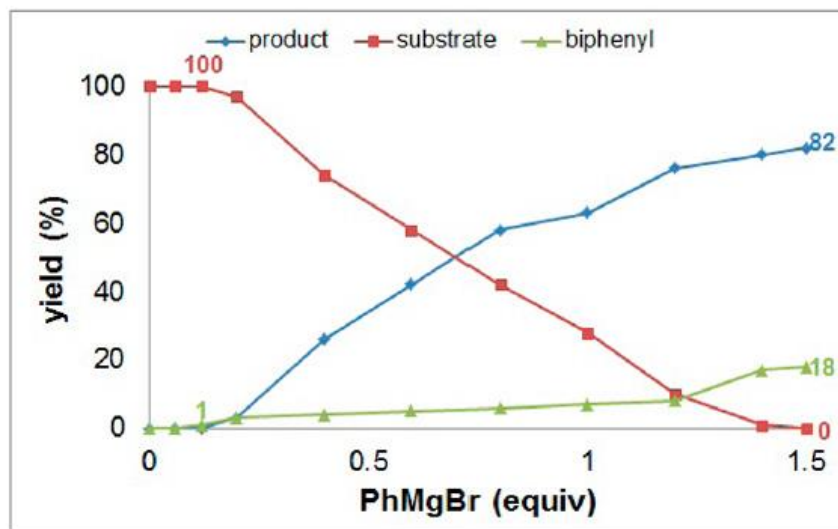
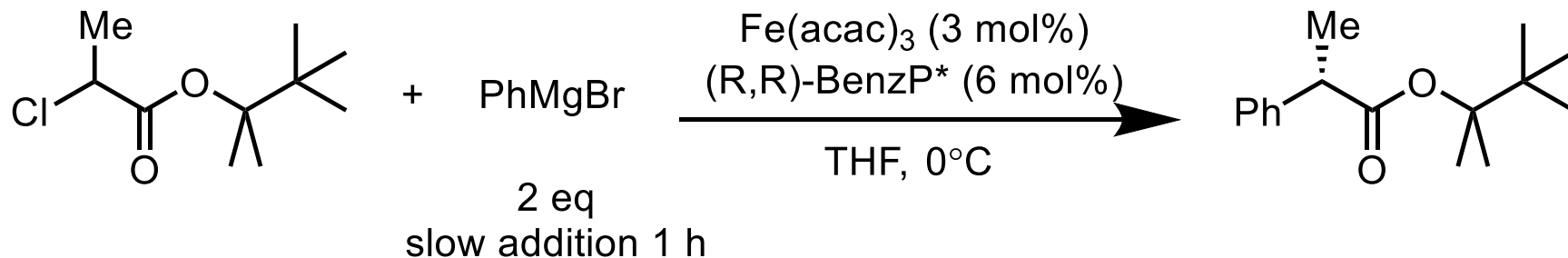
- **First iron-catalyzed enantioselective cross-coupling by Nakamura**



- Utilizing synthetically versatile racemic  $\alpha$ -chloro- and  $\alpha$ -bromoalkanoates
- Enantio-induction by chiral BOX ligands was moderate, which achieve high enantioselectivities in Ni- or Co-catalyzed cross-coupling.

# Enantioselective Coupling

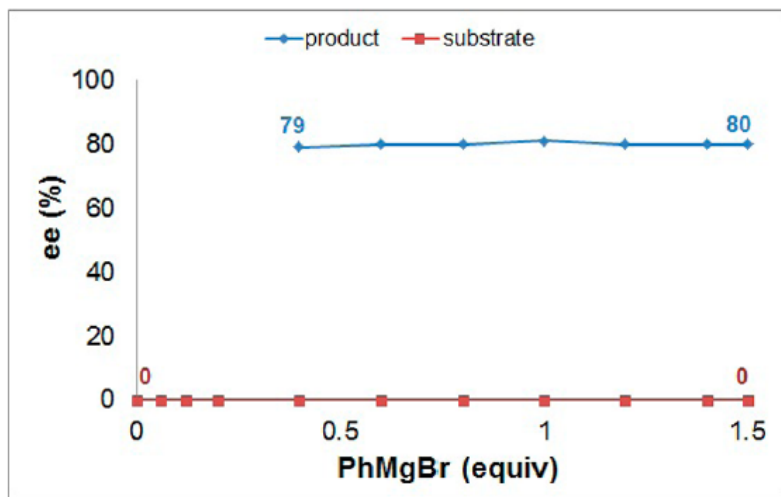
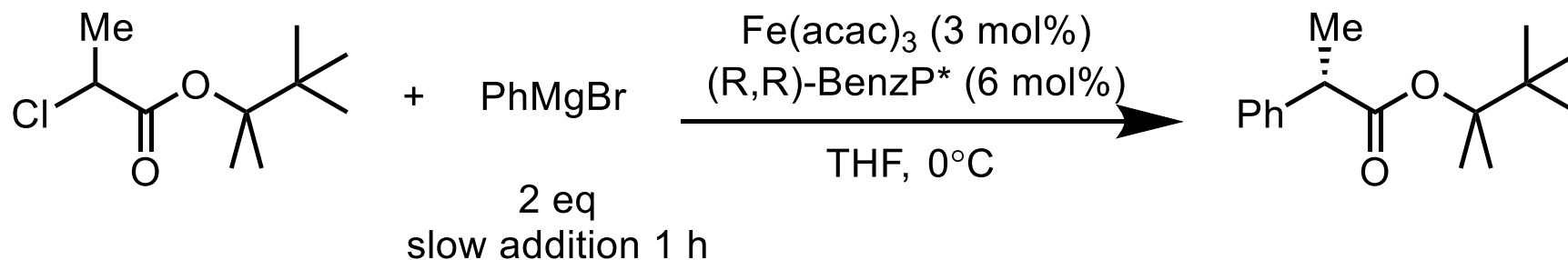
## • Time course analysis



- Addition of first 0.12eq PhMgBr  
→ No coupling product  
→ Partial reduction of Fe(III) prior to cross-coupling
- Following addition of PhMgBr  
→ The coupling reaction occurred.

# Enantioselective Coupling

- Time course analysis

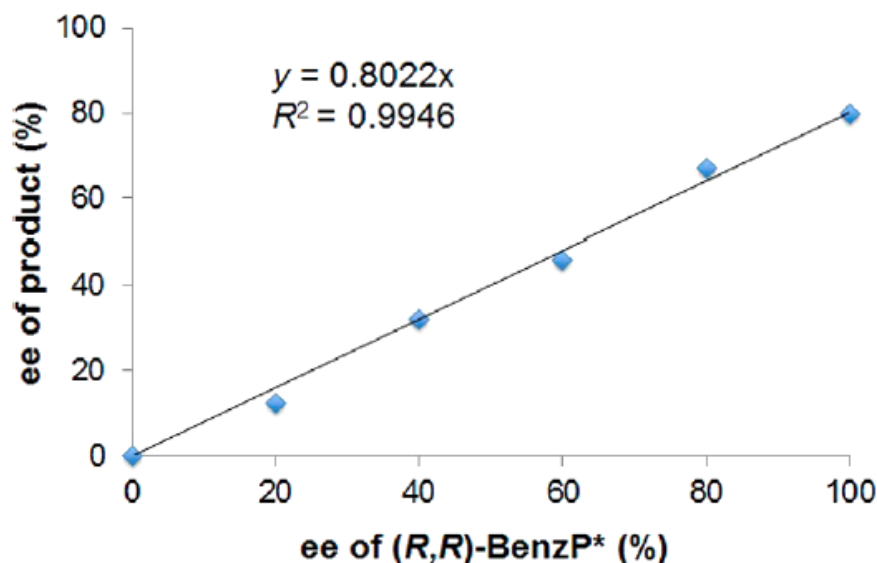


- Kinetic resolution was not observed.  
→ Suggesting that C-C bond forming is selectivity determining step



# Enantioselective Coupling

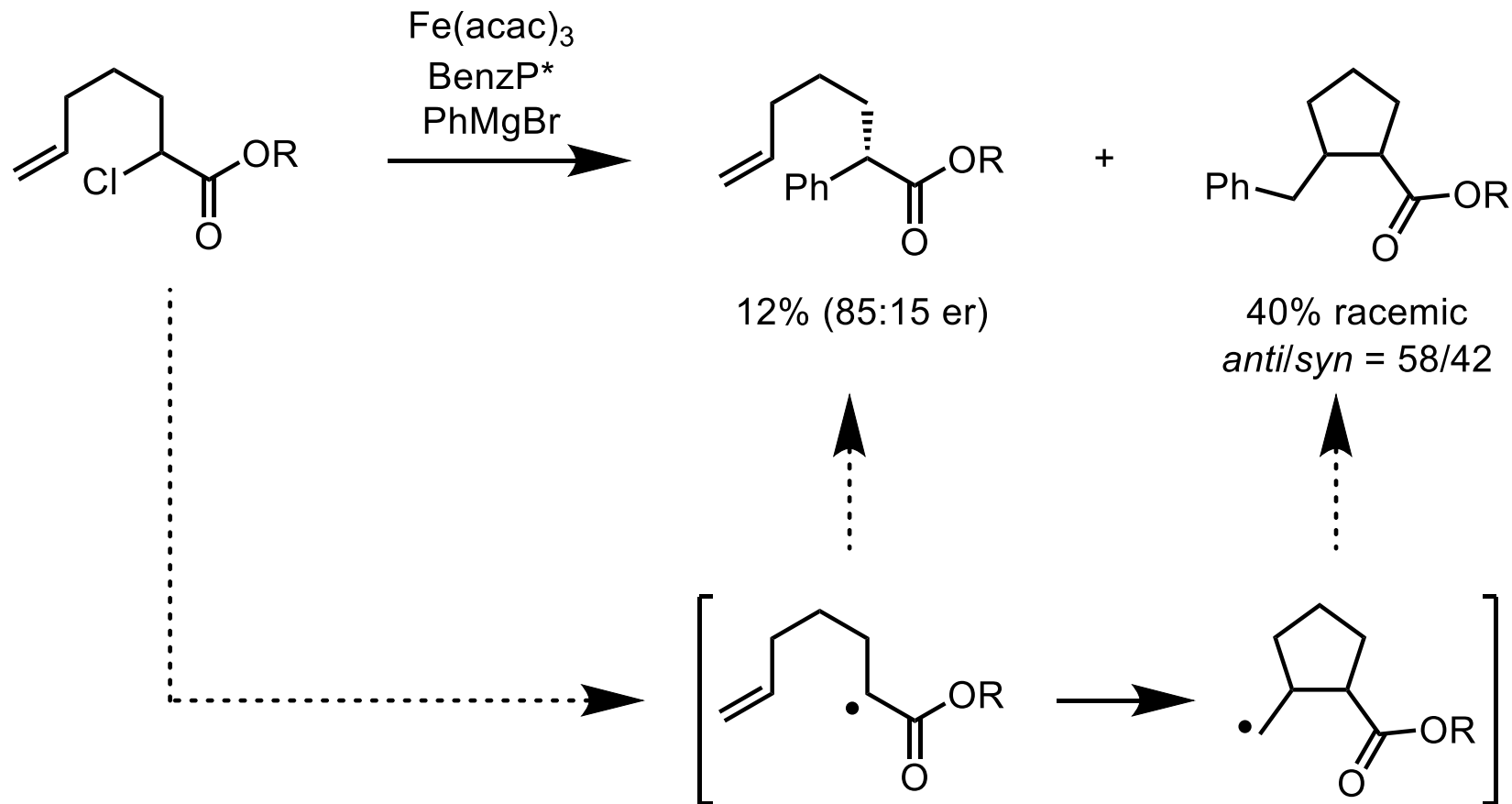
- Enantiomeric excess of the product is directly proportional to the enantiomeric excess of the ligand.



- Suggesting that the selectivity is determined under the influence of one chiral phosphine ligand which coordinates to one iron center

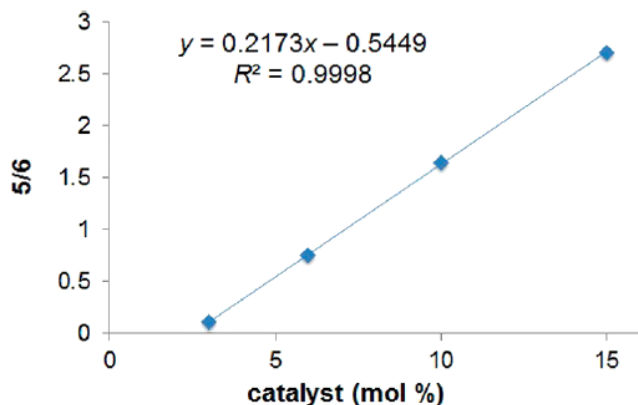
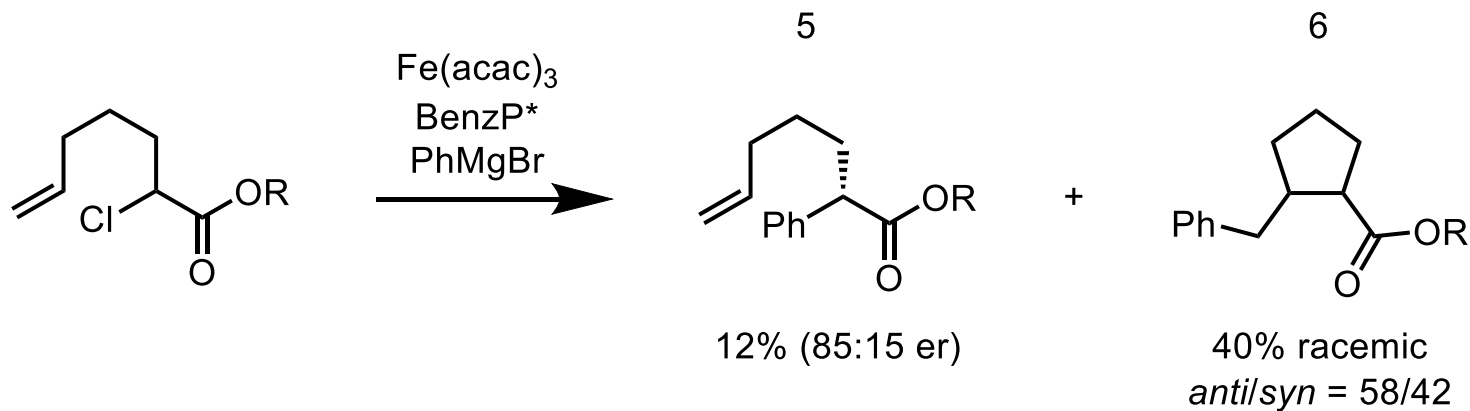
# Enantioselective Coupling

## • Radical probes



# Enantioselective Coupling

- The ratio of uncyclized/cyclized product is proportional to catalyst loading.



- Suggesting that formed alkyl radical escapes from solvent cage and undergoes sequential cyclization/arylation or direct arylation with aryl iron species.
- The cyclized product is racemic.  
→ cyclization occurs out of the chiral environment.



# Enantioselective Coupling

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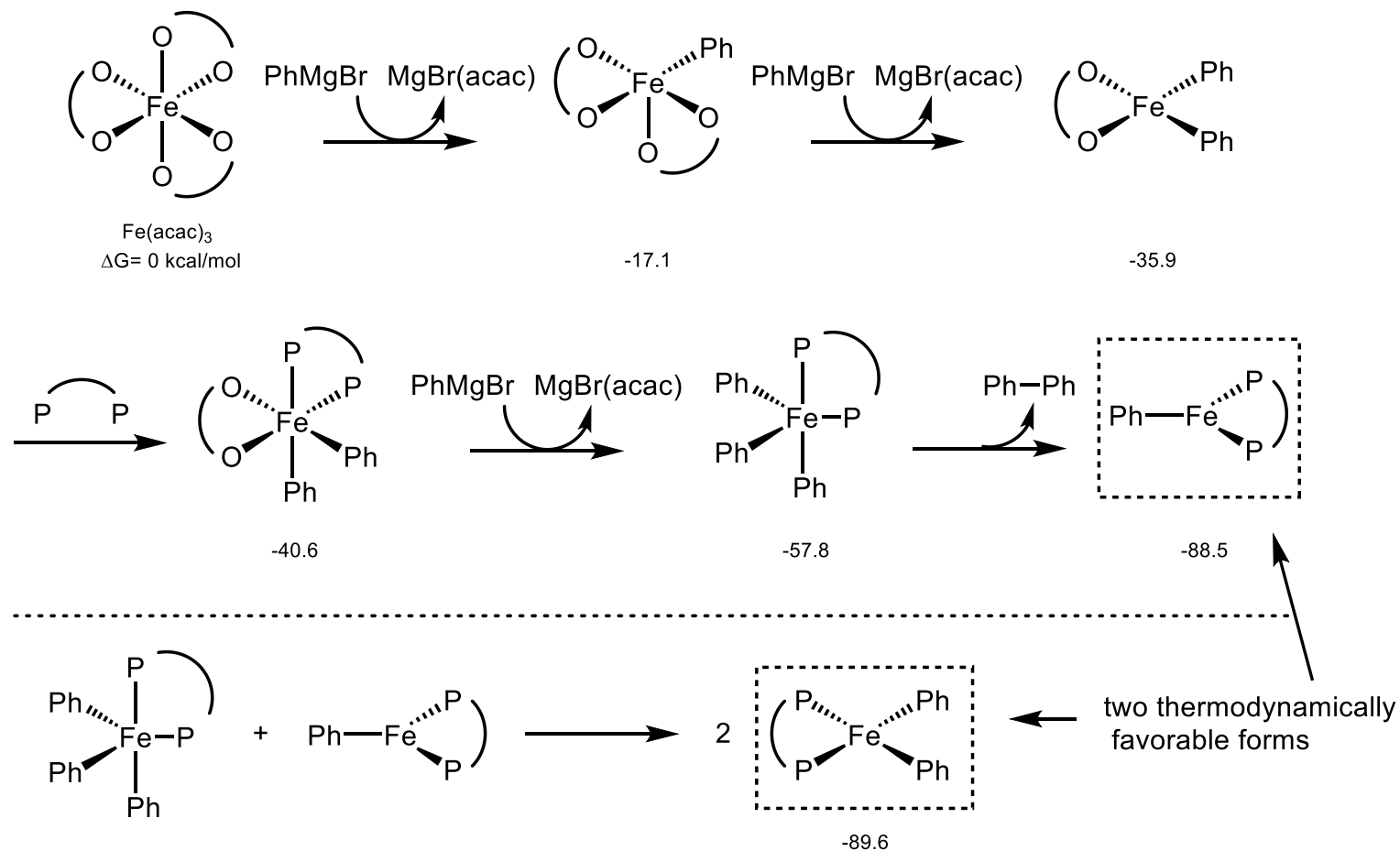
- In 2017 Nakamura also reported further mechanistic studies by DFT calculation.

The computational analysis consists of

- Pre-reactant iron complexes formation
- C-Cl bond activation
- Transmetalation
- C-C bond formation

# Enantioselective Coupling

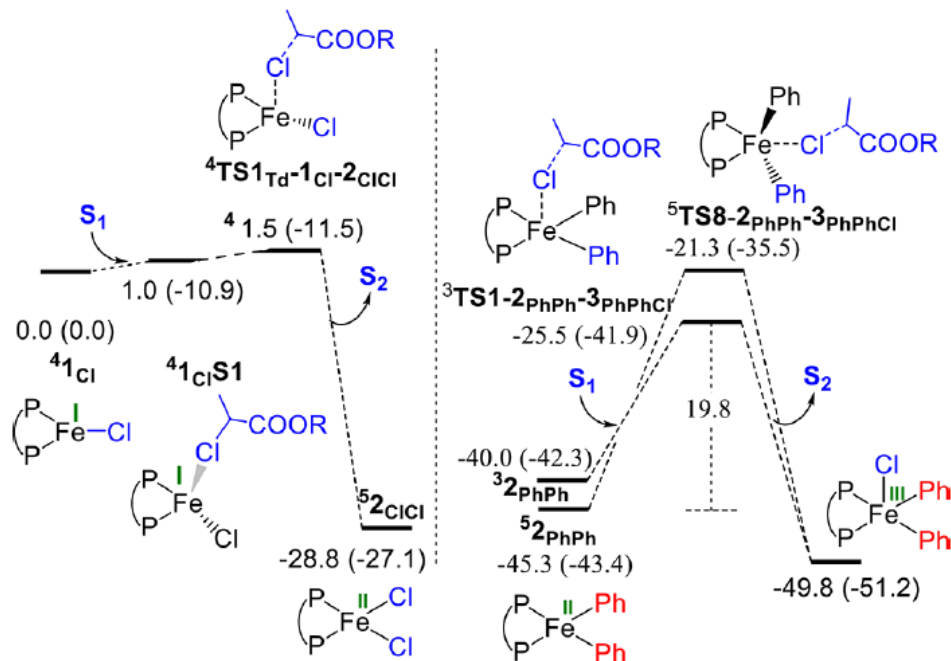
## • Pre-reactant iron complexes in solution



Sharma, A. K.; Sameera, W. M. C.; Jim, M.; Adak, L.; Okuzono, C.; Iwamoto, T.; Kato, M.; Nakamura, M.; Morokuma, K. *J. Am. Chem. Soc.* **2017**, *139*, 16117.

# Enantioselective Coupling

- C-Cl bond activation

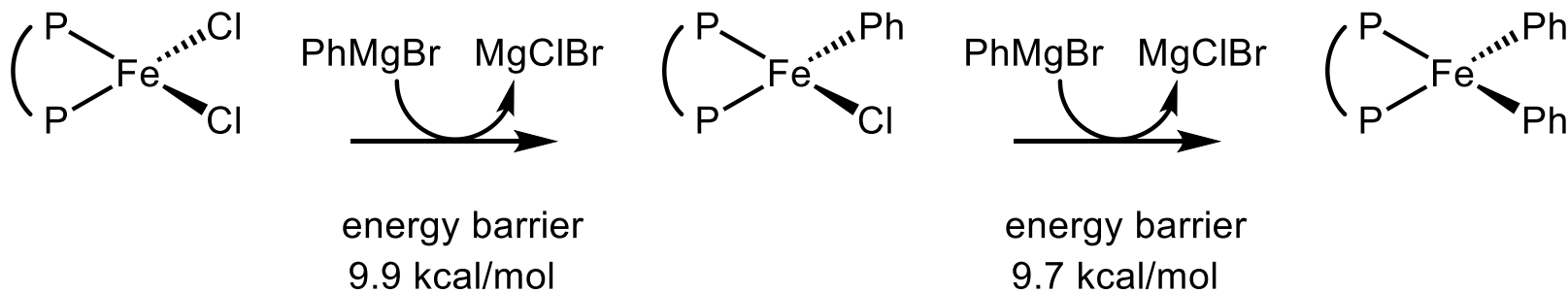


- Halogen abstraction by (BenzP\*)FeCl is almost barrierless process.
- The energy barrier of halogen abstraction by (BenzP\*)FePh is also low (5.0 kcal/mol).

→ Fe(I) species would be active species for C-Cl activation.

# Enantioselective Coupling

- Transmetalation



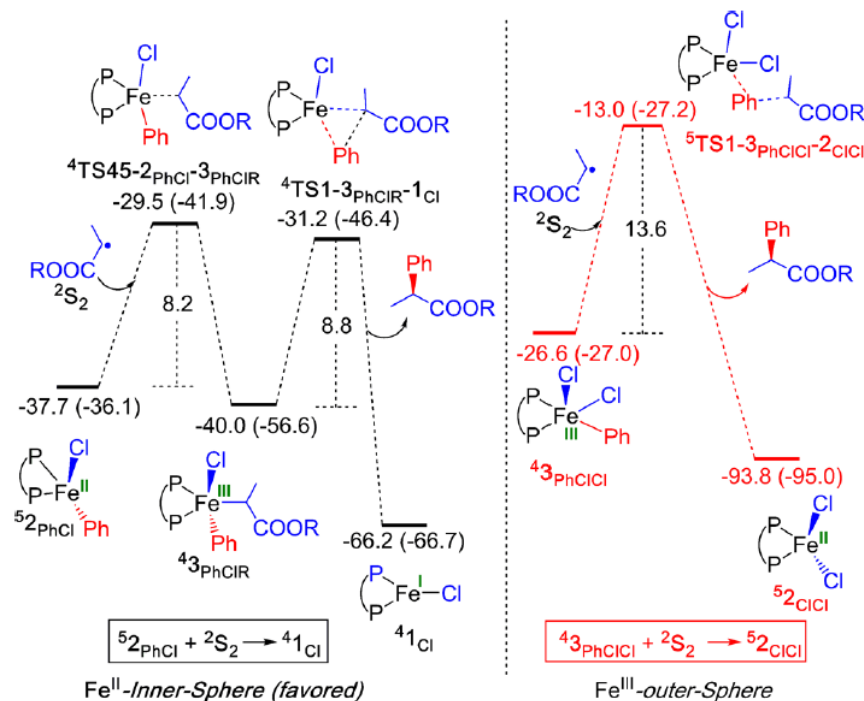
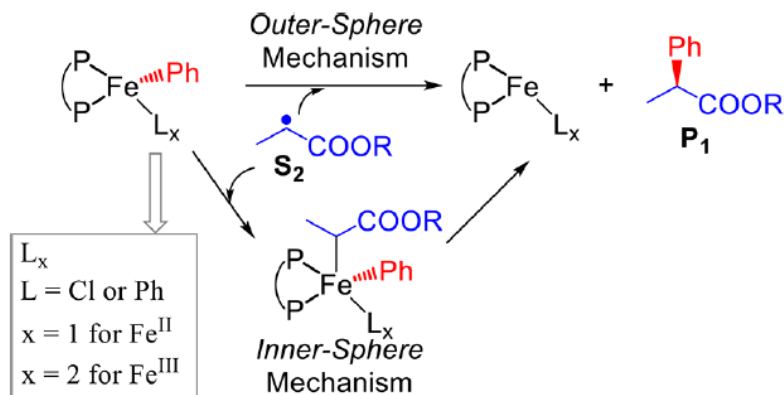
- Both processes can be possible under reaction conditions.



# Enantioselective Coupling

- C-C bond formation

- Two possible mechanisms

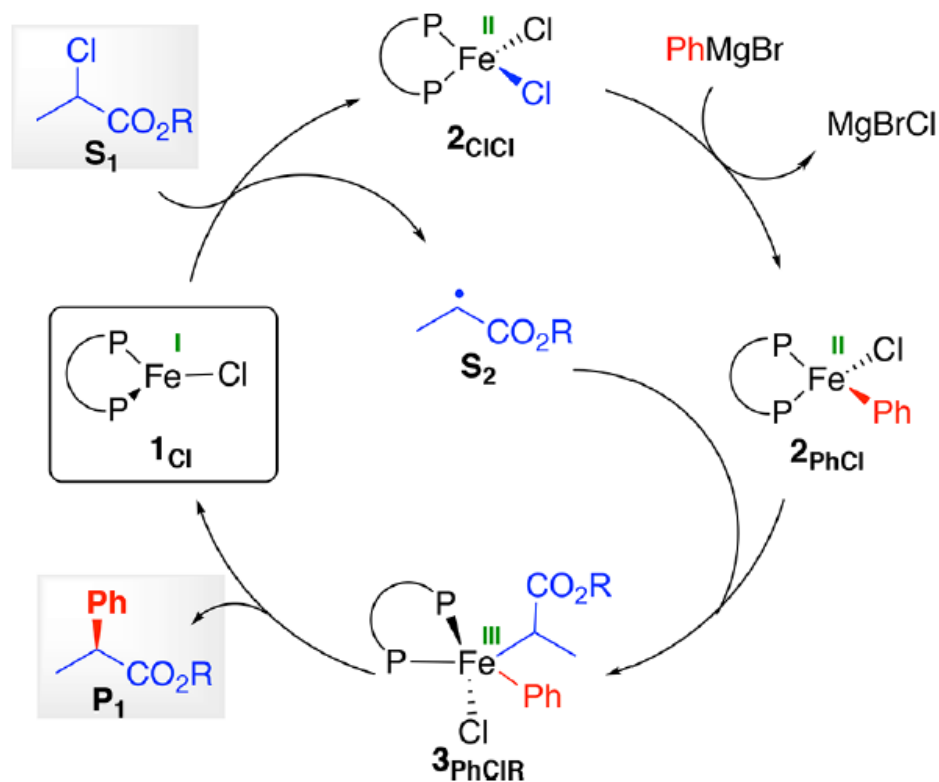


- Energy barrier: Inner-sphere mechanism 8.8 kcal/mol < Outer-sphere mechanism 13.6 kcal/mol

→ Inner-sphere mechanism is favorable.

# Enantioselective Coupling

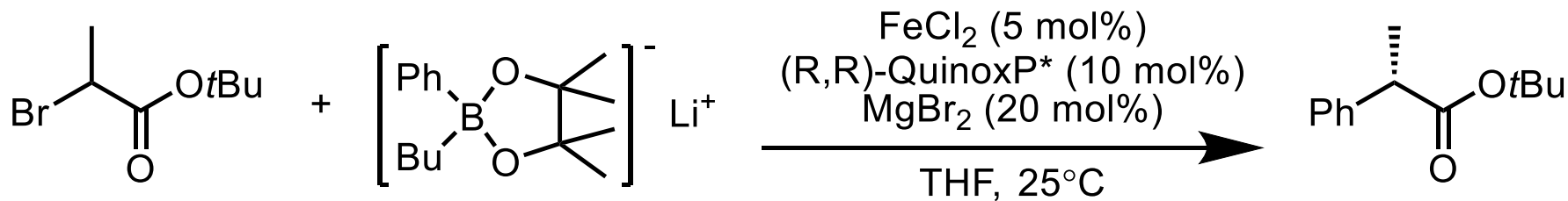
- New proposal for the mechanism



Sharma, A. K.; Sameera, W. M. C.; Jim, M.; Adak, L.; Okuzono, C.; Iwamoto, T.; Kato, M.; Nakamura, M.; Morokuma, K. *J. Am. Chem. Soc.* **2017**, *139*, 16117.

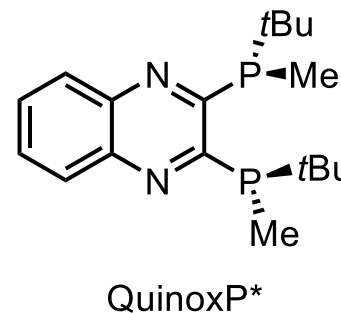
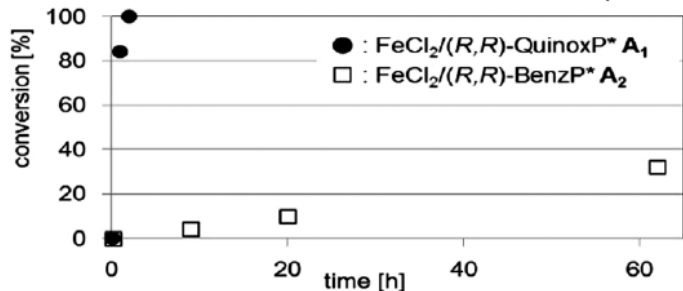
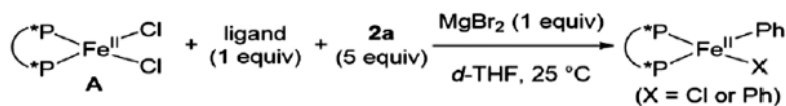
# Enantioselective Coupling

## • Iron-catalyzed enantioselective Suzuki coupling



99% yield  
84:16 er

## • Mechanistic investigation



- Electron-withdrawing nature of the ligand backbone makes iron centre more electrophilic and accelerates the transmetalation.

# Summary

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- Iron-catalyzed cross-coupling reactions are attractive due to their many favorable features.
- Mechanistic insight is lacking because of the nature of iron.
- The iron-catalyzed cross-coupling reactions are rapidly developing, and further study will be hoped.