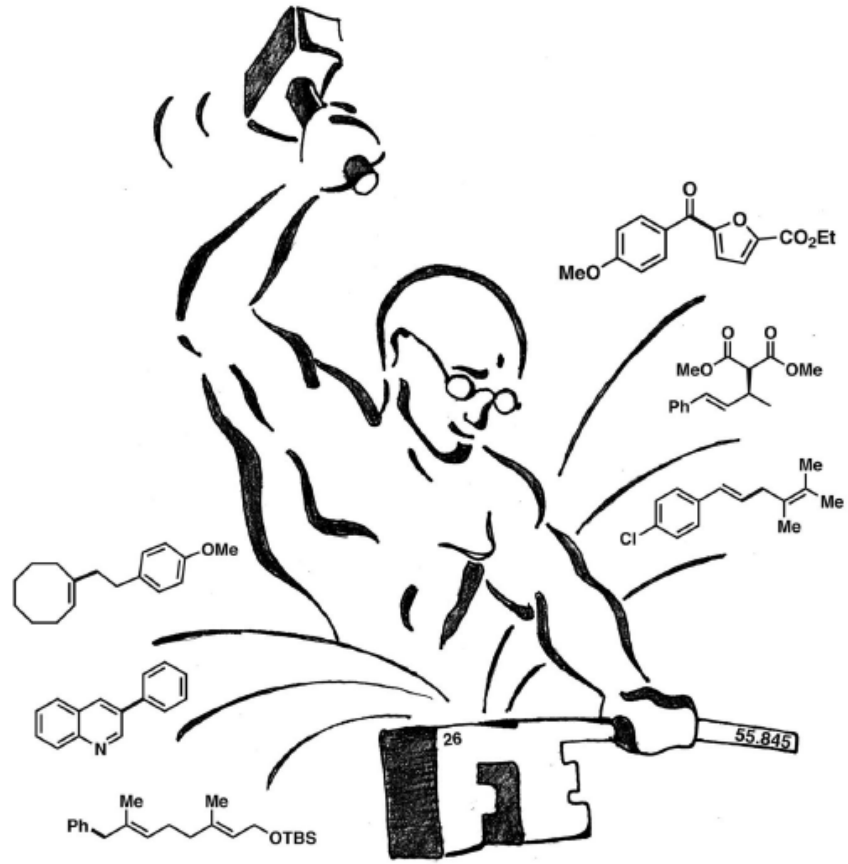
# *Recent Developments in Iron-Catalyzed Cross-Coupling*



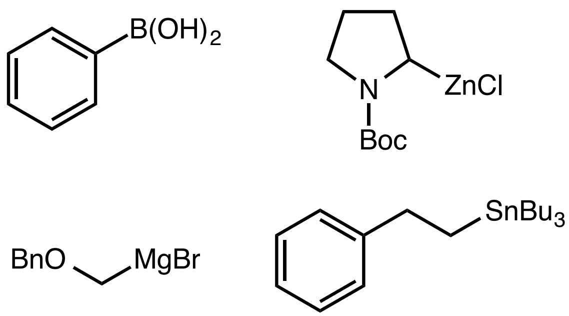

Artwork by von Wangelin design (Rostock, Germany)

Jack Terrett
MacMillan Group Meeting
March 15th, 2016

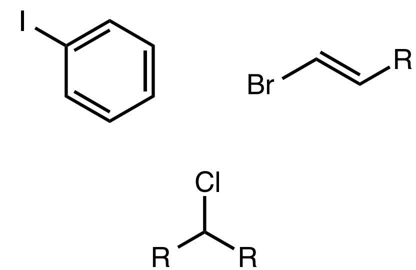
## *Transition Metal-Catalyzed Cross-Coupling*

- One of the most fundamental class of reactions in organic synthesis for C–C bond formation

***organometallic nucleophiles***

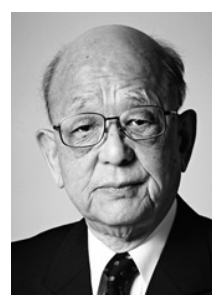



***organometallic electrophiles***




- 2010 Nobel Prize awarded in this area: Heck, Negishi, and Suzuki






# *Metal-Catalyzed Cross-Coupling*

■ One of the most fundamental reactions in organic synthesis for C–C bond formation

***diverse nucleophile handles***

**Mg** = Kumada

**Zn** = Negishi

**B** = Suzuki-Miyaura

**Sn** = Stille

**Si** = Hiyama

***transition metal catalysts***

46
**Pd**
**Palladium**
106.42

28
**Ni**
**Nickel**
58.693

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***What about iron catalysis?***

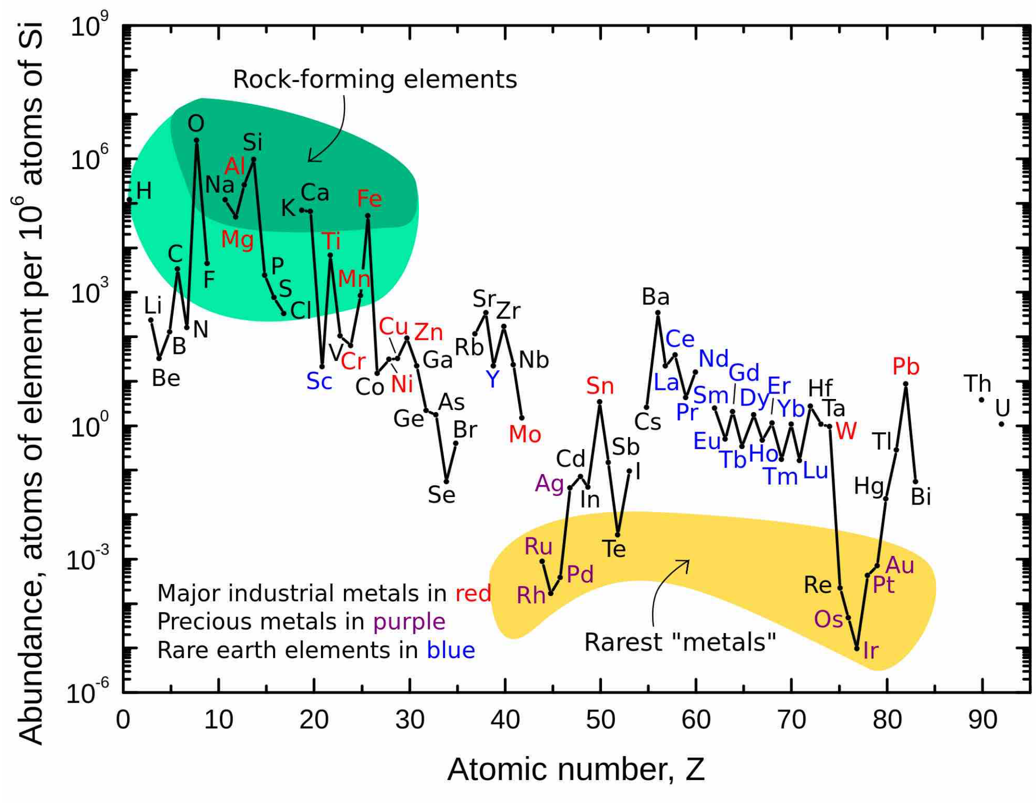
26
**Fe**
**Iron**
55.847

# Why Iron Catalysis?

■ Compared to palladium and nickel, iron has many beneficial characteristics

***Iron is second most abundant metal in the Earth's crust***

***4.7 wt% vs. 1x10$^{-6}$ wt% for Pd***



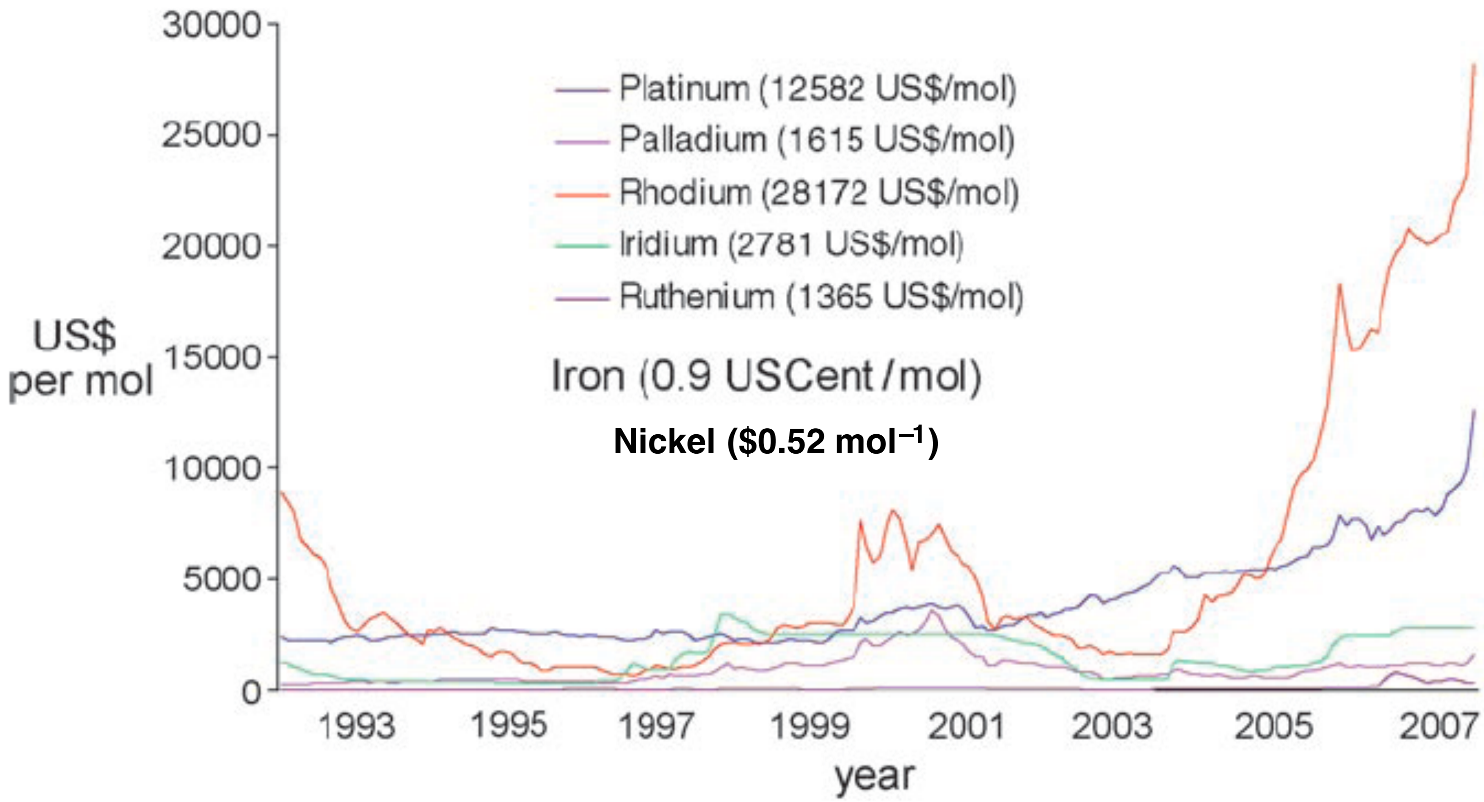

https://en.wikipedia.org/wiki/Abundance_of_the_chemical_elements

Renner, H.; Schmuckler, G. *Metals and their compounds in the environment.*, ed. E Merian, Wiley-VCH, Weinheim, 1991.

# *Why Iron Catalysis?*

■ Compared to palladium and nickel, iron has many beneficial characteristics

***Iron is far more inexpensive than palladium***



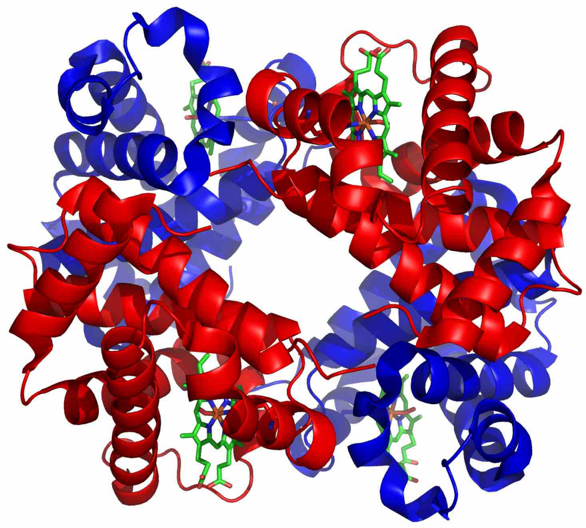

http://www.icmj.com/current-metal-prices.php

Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3317.

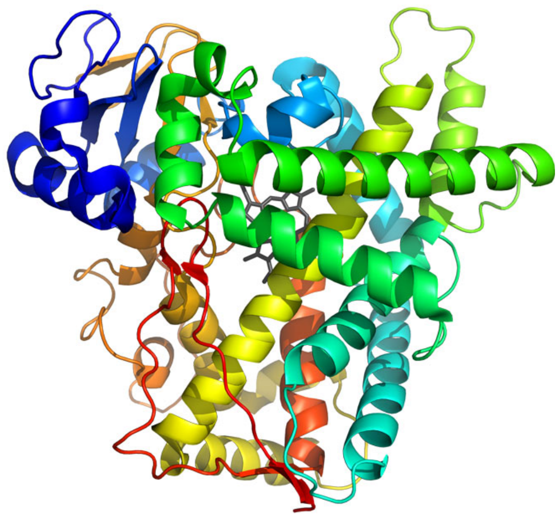
# *Why Iron Catalysis?*

■ Compared to palladium and nickel, iron has many beneficial characteristics

***Iron is relatively non-toxic compared to palladium and nickel***



**Haemoglobin**



**Cytochrome P450**

***Iron is present in a large number of biological systems, notably metalloproteins***

https://en.wikipedia.org/wiki/Hemoglobin

http://scottlab.info/illustration/human-cytochrome-p450-2a13/

# *Why Iron Catalysis?*

- Compared to palladium and nickel, iron has many beneficial characteristics

***1) Abundance: Iron is second most abundant metal in the Earth's crust***

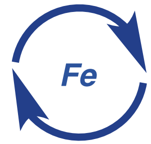
***2) Cost: Iron is far more inexpensive than palladium***

***3) Toxicity: Iron is relatively non-toxic compared to palladium and nickel***

***4) Reactivity!***

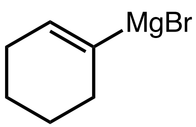
***Can we discover new reactivity that is unique to iron catalysis?***

# *Iron-Catalyzed Cross-Coupling*




## Kumada Coupling

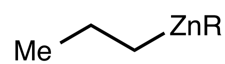
*Mg*




***Grignard reagents***

## Negishi Coupling

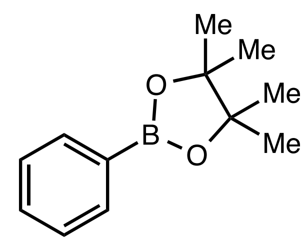
*Zn*




***organozincs***

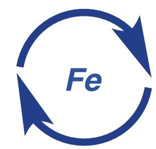
## Suzuki Coupling

*B*



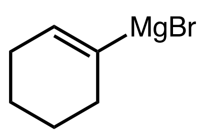

***organoboron***

# *Iron-Catalyzed Cross-Coupling*




## Kumada Coupling

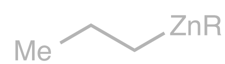
*Mg*




***Grignard reagents***

## Negishi Coupling

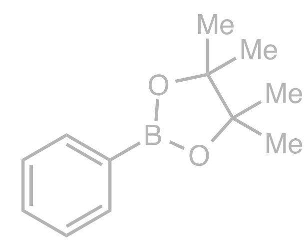
*Zn*




***organozincs***

## Suzuki Coupling

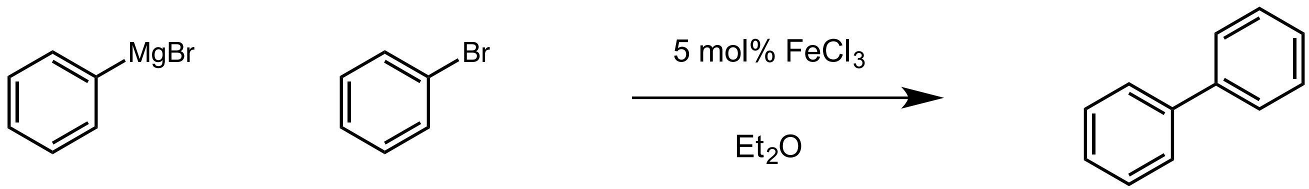
*B*




***organoboron***

# *Iron-Catalyzed Cross-Coupling*

■ First report of iron-mediated cross-coupling came from Kharasch and Fields in 1941




***47% yield***

■ Reactivity is observed in the presence of $CoCl_2$, $FeCl_3$, $MnCl_2$, and $NiCl_2$

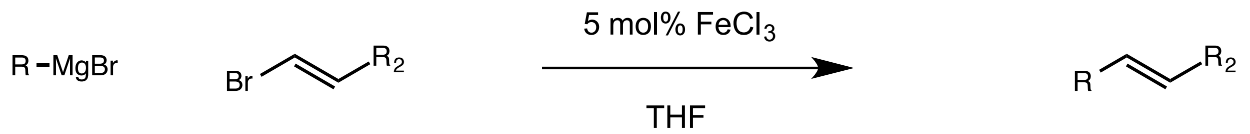
■ Kharasch proposes that the metallic halide gets reduced to a lower oxidation state by the Grignard reagent

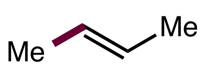
***It was another 30 years until the field really got started.***

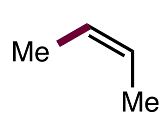
Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316.

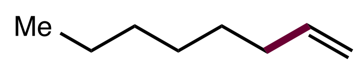
# *Iron-Catalyzed Cross-Coupling*

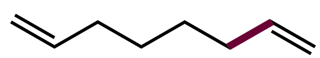
■ Kochi reported the coupling of alkenyl halides with Grignard reagents in 1971



***>95% yield*** ***>95% yield*** ***83% yield*** ***64% yield***

*(trans reacts ~15 times faster than cis)*

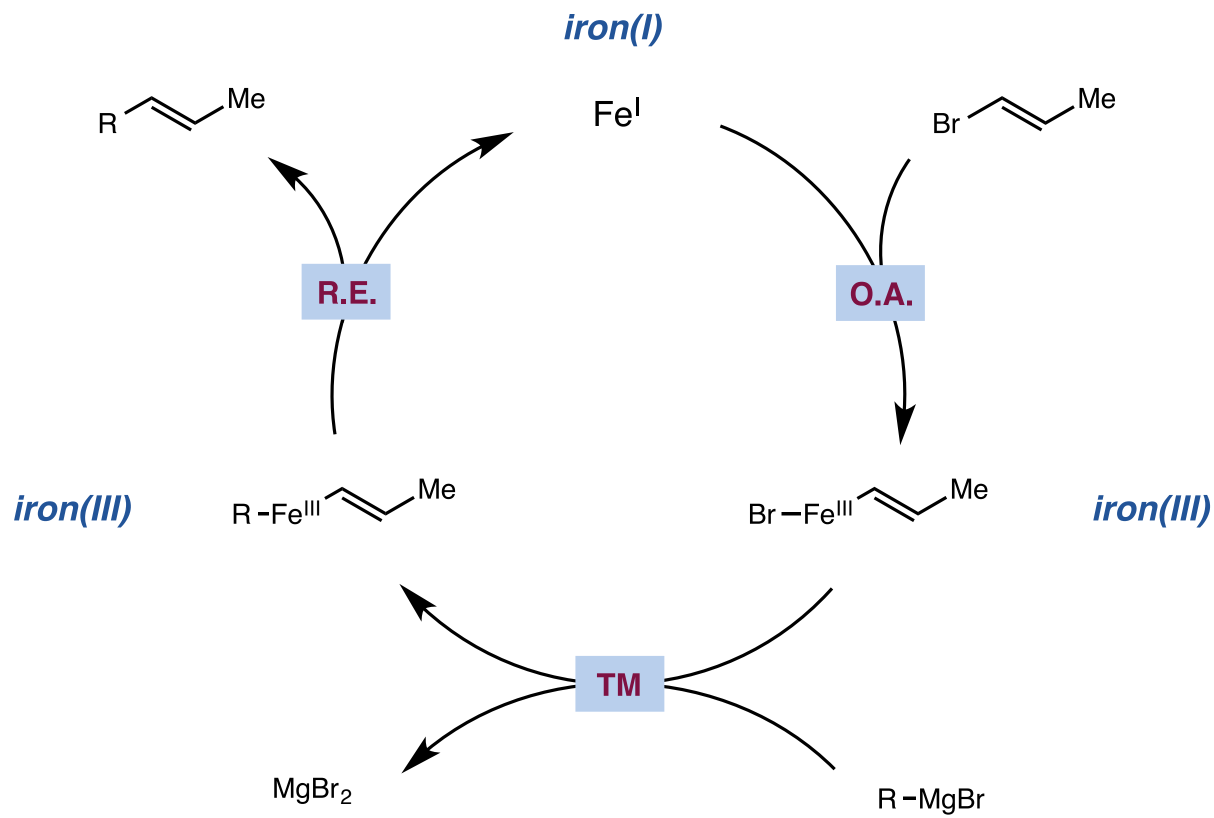
***coupling of alkenyl halides occurs stereospecifically***


Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1487.

Tamura, M.; Kochi, J. *Synthesis* **1971**, *1971*, 303.

# *Iron-Catalyzed Cross-Coupling*

■ Kochi proposed an Fe(I)/(III) mechanistic cycle

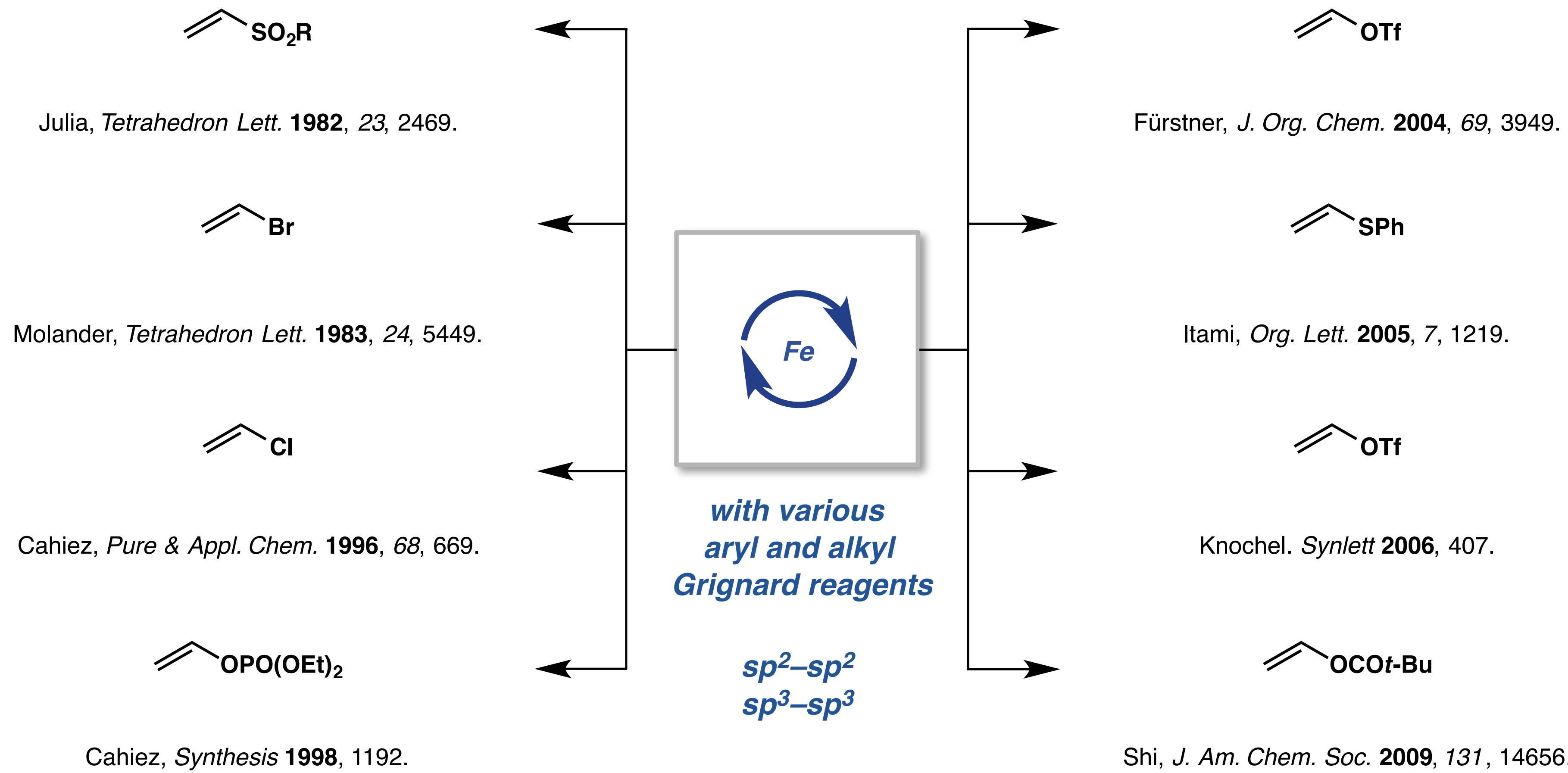



***active Fe(I) formed by reduction of Fe(III) precatalyst by Grignard reagent***

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

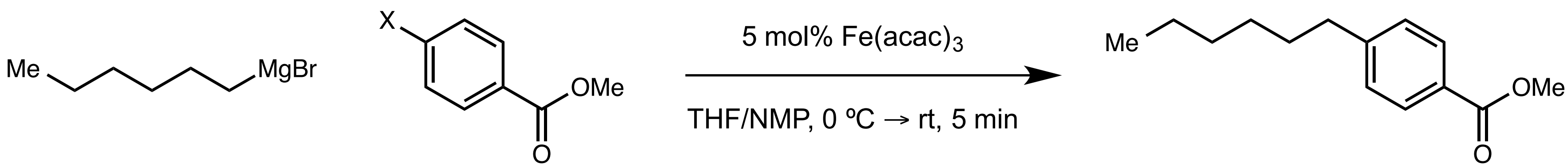
# *Iron-Catalyzed Cross-Coupling*

■ Following Kochi's report, Fe-catalyzed couplings with alkenyl electrophiles developed rapidly



# *Iron-Catalyzed Cross-Coupling*

■ Fürstner reported first coupling of aryl electrophiles with Grignard reagents in 2002




X = Cl, OTf, OTs

| X | Product | ArH |
|---|---|---|
| I | 27% | 46% |
| Br | 38% | 50% |
| Cl | >95% | 0% |
| OTf | >95% | 0% |
| OTs | >95% | 0% |

***arene reduction possibly due to a radical decomposition pathway***

***effectiveness of Ar–Cl is suggestive of Fe(–II) active catalyst for oxidative addition***

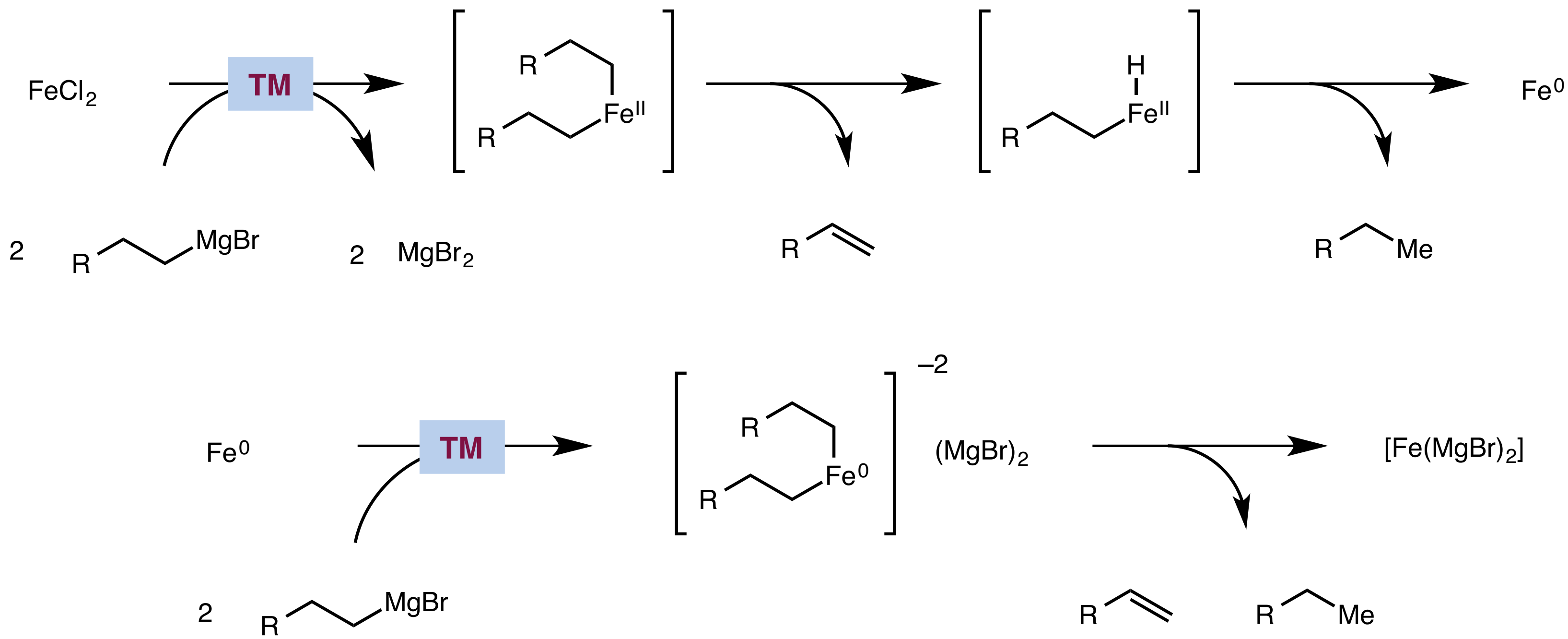

Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609.

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

# *Iron-Catalyzed Cross-Coupling*

## ■ Fürstner proposed a Fe(–II)/(0) mechanistic cycle

**[Fe(MgX)$_2$] active catalyst is prepared in situ from FeCl$_2$ and 4 equiv. RMgBr**




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

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

# *Iron-Catalyzed Cross-Coupling*

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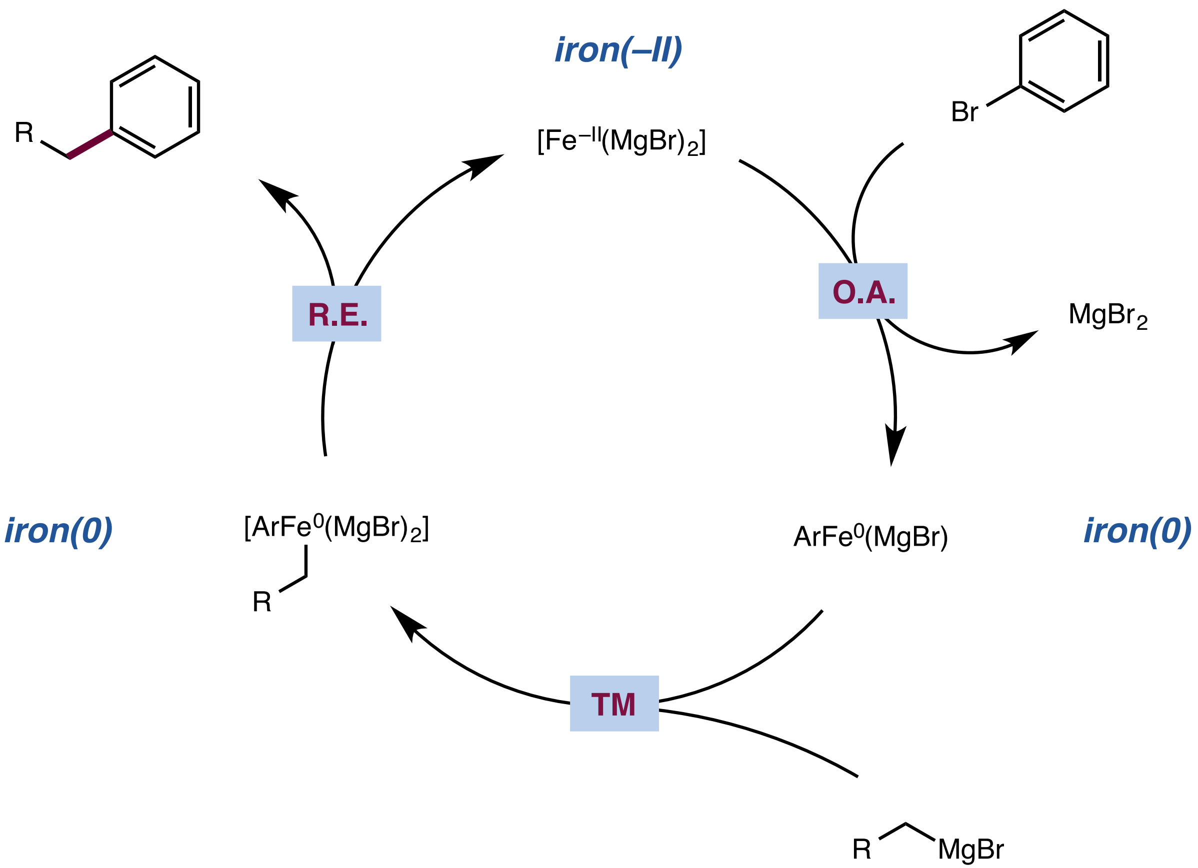


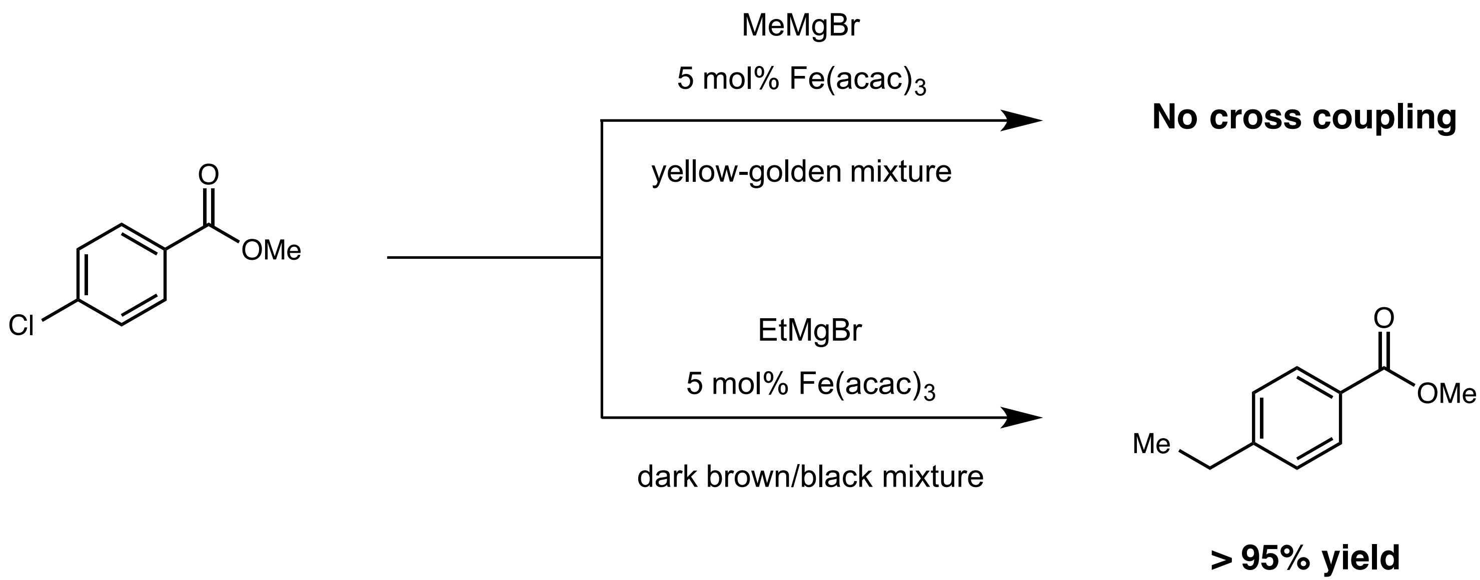


Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609.

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

# *Iron-Catalyzed Cross-Coupling*

■ Cross-coupling shuts down in when MeMgBr is employed




***supports proposed active Fe(–II) catalyst as β-hydride elimination is required***

***in the presence of Fe(0), no reactivity is observed - restored upon addition of excess Grignard***


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

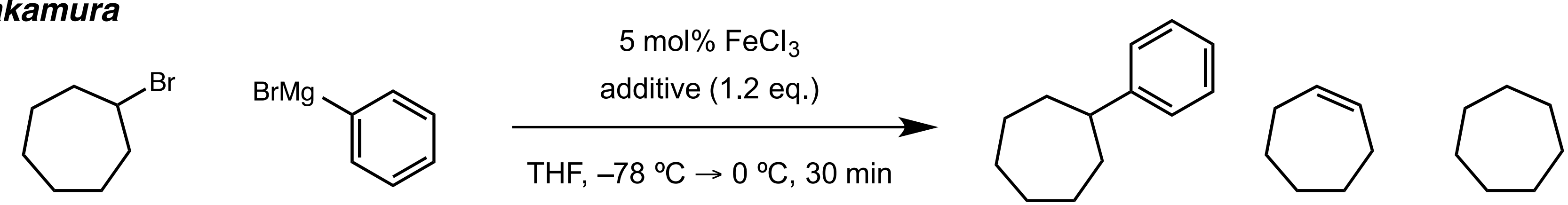
Fürstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

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

# *Iron-Catalyzed Cross-Coupling*

■ In 2004, Nakamura, Hayashi, and Fürstner report coupling of alkyl halides with aryl Grignards

***Nakamura***



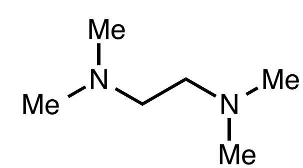

**1** **2** **3** **4**

***Table 1.*** Effect of Additives on the Product Selectivity and Yield

| entry | additive | % yield[a] 2 | 3 | 4 | 1 | Ph–Ph |
|---|---|---|---|---|---|---|
| 1 | none | 5 | 79 | 0 | 4 | 6 |
| 2 | $Et_3N$ | 3 | 78 | 0 | 11 | 5 |
| 3 | *N*-methyl morpholine | 8 | 72 | 0 | 4 | 5 |
| 4 | DABCO | 20 | 2 | 0 | 75 | 3 |
| 5 | NMP | 15 | 3 | trace | 79 | 4 |
| 6 | TMEDA | 71 | 19 | 3 | trace | 10 |

***bidentate TMEDA ligand suppressed competing β-hydride elimination***

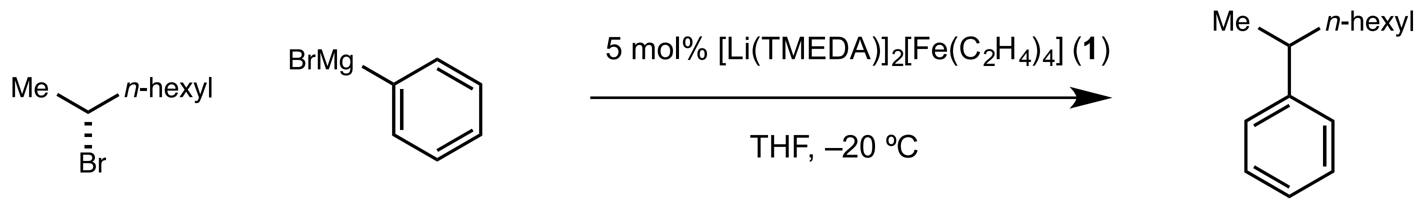
TMEDA =




Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686.
Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.
Fürstner, A.; Martin, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955.

## Nakamura and Fürstner propose a radical-based mechanism

***Fürstner***




***94% yield racemate***

***98% ee***

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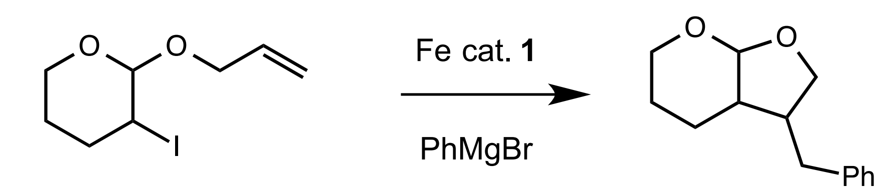
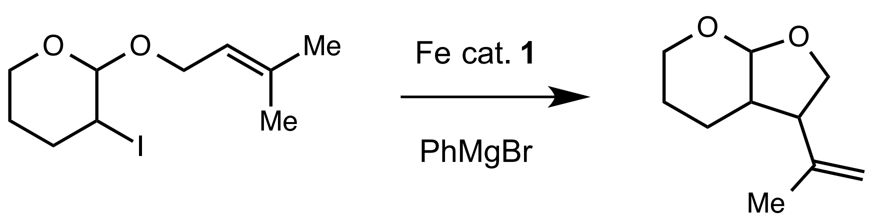



***85% yield***

***cyclization suggests intermediacy of radicals***




***77% yield***

***no cross-coupling observed from 3º radical***

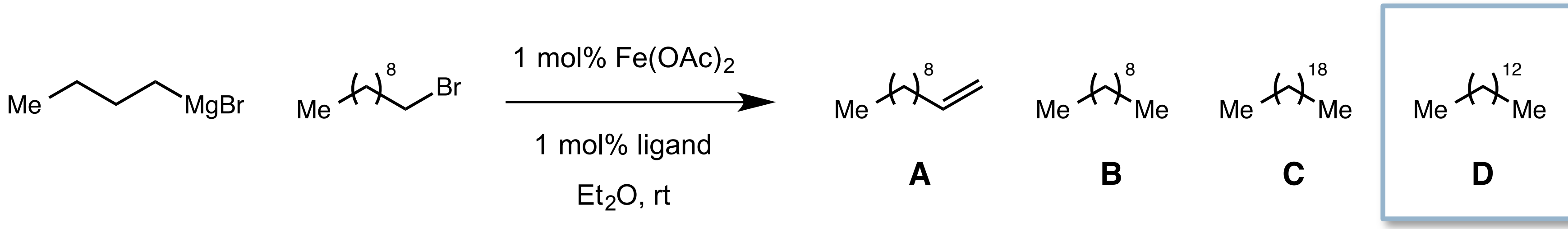
Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686.

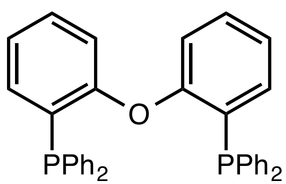
Fürstner, A.; Martin, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955.

# *Iron-Catalyzed Kumada Cross-Coupling*

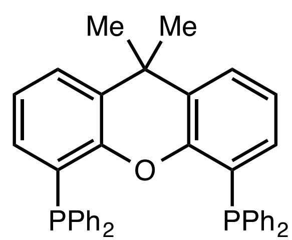
## ■ Chai demonstrated the first *sp³–sp³* coupling using Fe catalysis

■ One of the greatest challenges is overcoming competing homocoupling and β-hydride elimination




**1**




**2**

| | A | B | C | D |
|---|---|---|---|---|
| **1** | **10%** | **62%** | **13%** | **5%** |
| **2** | **2%** | **31%** | **10%** | **51%** |

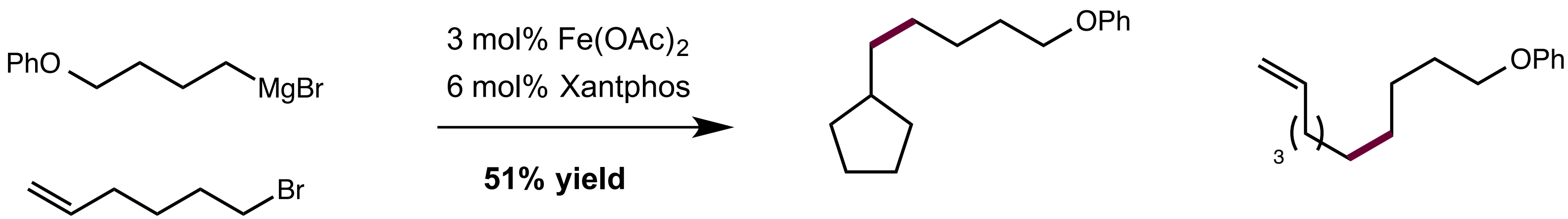
***use of Xantphos (2) reduced byproduct formation***

Dongol, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015.

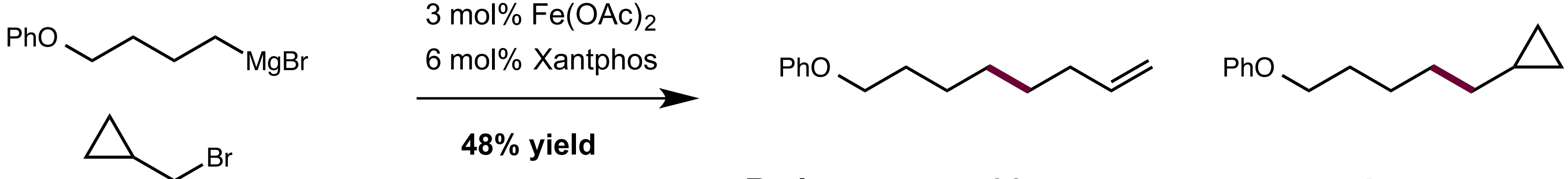
# *Iron-Catalyzed Kumada Cross-Coupling*

## ■ Chai demonstrated the first *sp*$^3$–*sp*$^3$ coupling using Fe catalysis

■ A radical mechanism is proposed for this *sp*$^3$–*sp*$^3$ Kumada coupling




**Ratio: 95 5**




**Ratio: > 96 < 4**

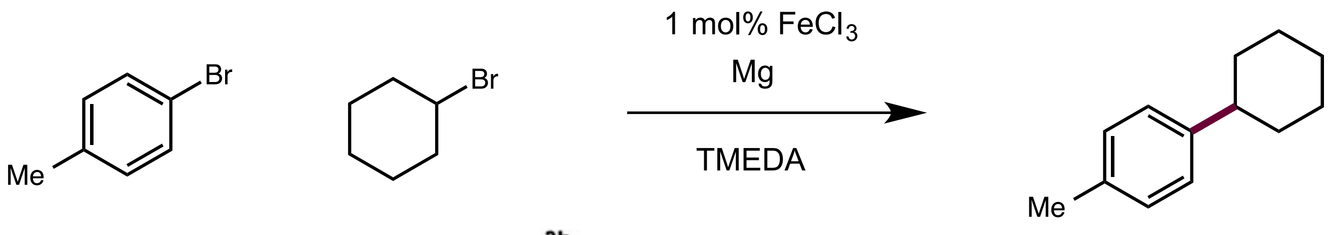
***results suggest alkyl radicals are formed from the corresponding alkyl halides***

Dongol, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015.

# *Iron-Catalyzed Cross-Coupling*

## Von Wangelin accomplished an iron-catalyzed cross electrophile coupling

- Domino iron catalysis: iron-catalyzed Grignard formation followed by cross-coupling




**3b**

***75% yield***

14% Ar–Ar

**4b = 4,4'-bitolyl**

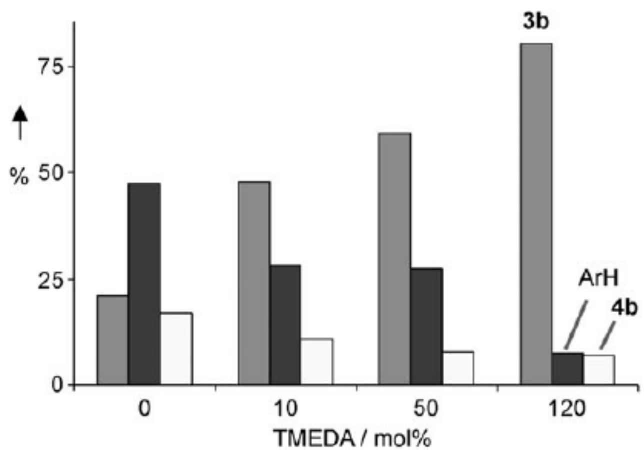



***Figure 1.*** TMEDA dependence of the model system *p*-tolyl bromide (**1a**) and *n*-dodecyl bromide (**2b**). ArH = toluene.

***selectivity depends greatly on TMEDA loading, possibly stabilizes Fe and Mg complexes***

***increased TMEDA = slower formation of Grignard reagent***

Czaplik, W. M.; Mayer, M.; von Wangelin, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 607.

# *Iron-Catalyzed Cross-Coupling*

- Von Wangelin accomplished an iron-catalyzed cross electrophile coupling
  - The intermediacy of both Grignard species (aryl and alkyl) is proposed
  - Formation of both Grignard species is accelerated in the presence of $FeCl_3$

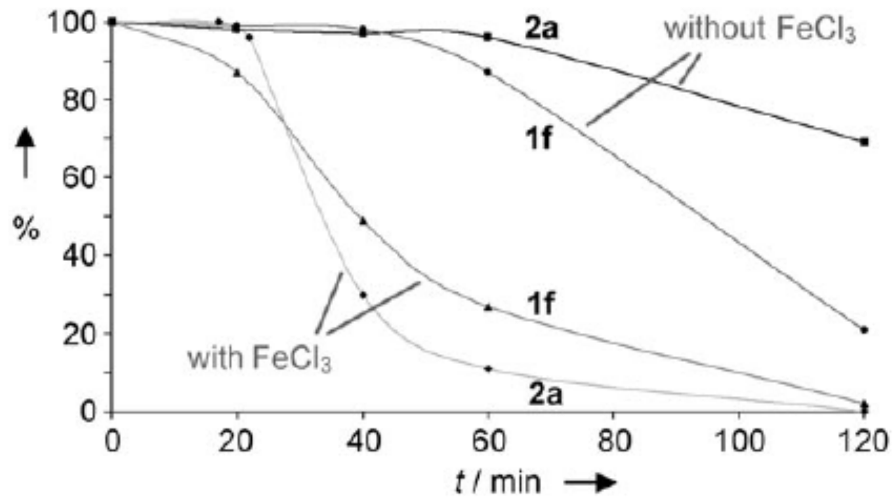


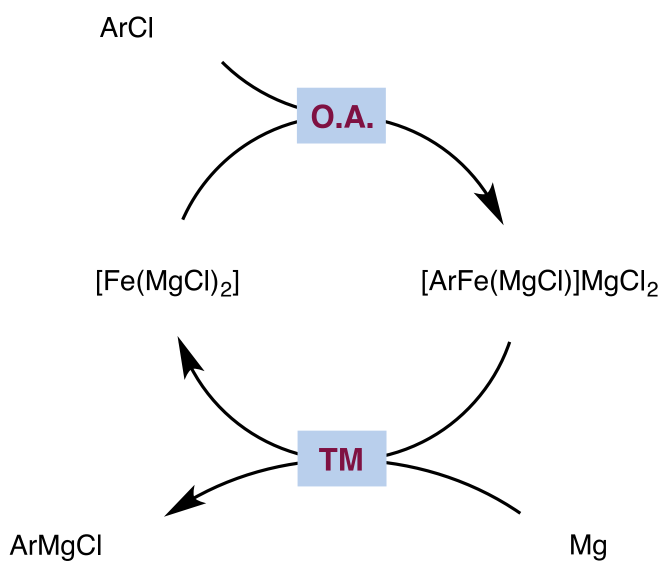

***Figure 2.*** Iron-catalyzed Grignard formation from 1-bromonaphthalene (**1f**) and cyclohexyl bromide (**2a**).

Czaplik, W. M.; Mayer, M.; von Wangelin, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 607.

# *Iron-Catalyzed Cross-Coupling*

## ■ Von Wangelin accomplished an iron-catalyzed cross electrophile coupling

- ■ The intermediacy of both Grignard species (aryl and alkyl) is proposed
- ■ Formation of both Grignard species is accelerated in the presence of $FeCl_3$
- ■ Bogdanovic has shown that $[Fe(MgX)_2]$ catalyzes formation of Grignards from aryl halides and Mg





Bogdanovic, B.; Schwickardi, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4610.

Czaplik, W. M.; Mayer, M.; von Wangelin, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 607.

# Iron-Catalyzed Cross-Coupling

- Von Wangelin accomplished an iron-catalyzed cross electrophile coupling
  - The intermediacy of both Grignard species (aryl and alkyl) is proposed
  - Formation of Grignard reagent appears to be rate-determining step

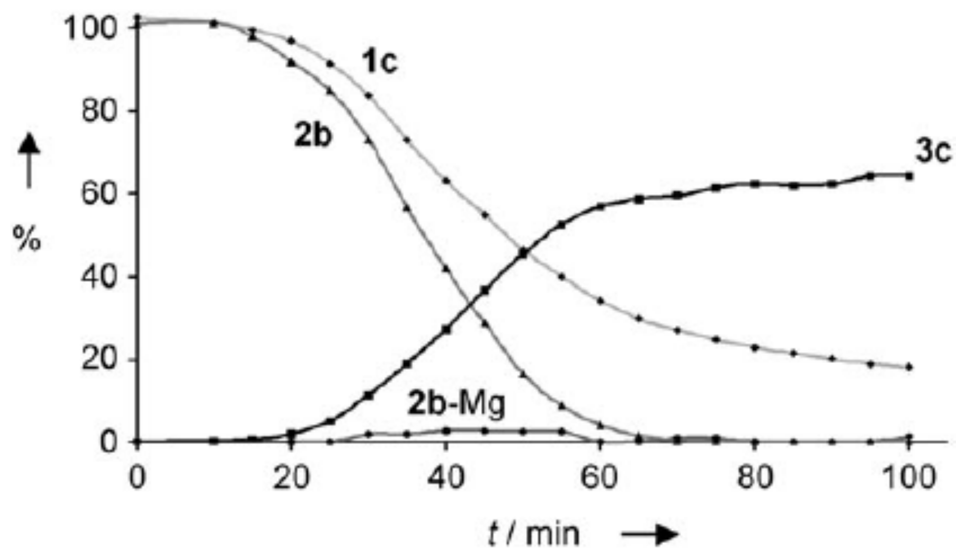
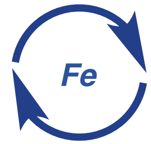



**Figure 3.** Concentration–time plots for the model reaction of 4-*tert*-butylbromobenzene (**1c**) and dodecyl bromide (**2b**) with intermediate **2b**–Mg.

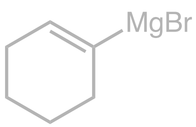
Czaplik, W. M.; Mayer, M.; von Wangelin, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 607.

# *Iron-Catalyzed Cross-Coupling*




## Kumada Coupling

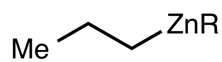
*Mg*




***Grignard reagents***

## Negishi Coupling

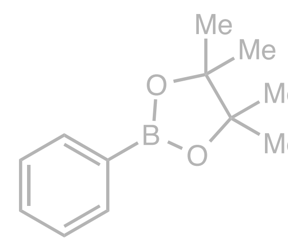
*Zn*




***organozincs***

## Suzuki Coupling

*B*

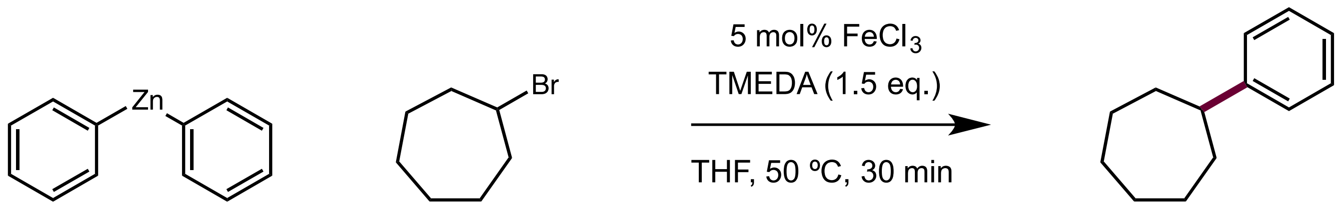



***organoboron***

# *Iron-Catalyzed Negishi Cross-Coupling*

## ■ Nakamura extended iron-catalyzed cross coupling to organozincs for milder protocol

■ Diorganozinc nucleophile was effective, but still required a magnesium salt

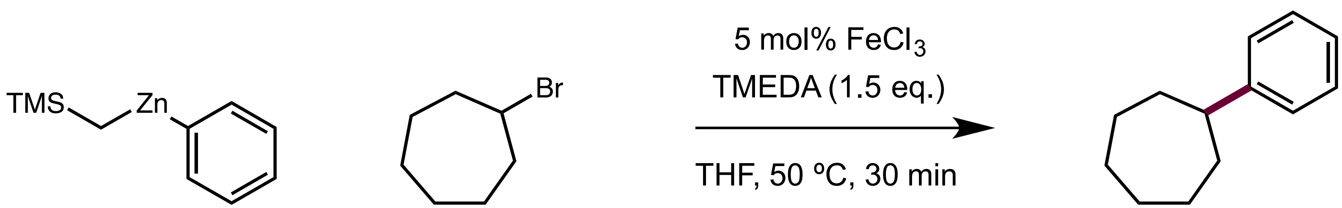



***96% yield***

***organozinc is prepared in situ from aryl Grignard and $ZnCl_2$***

***avoids the need for slow addition of Grignard reagent due to slower transmetallation of zinc to iron***

---




***95% yield***

***use of $TMSCH_2$ non-transferable ligand improves substrate economy***

Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, *11*, 1794.

# *Iron-Catalyzed Negishi Cross-Coupling*

## ■ Nakamura extended iron-catalyzed cross coupling to organozincs for milder protocol

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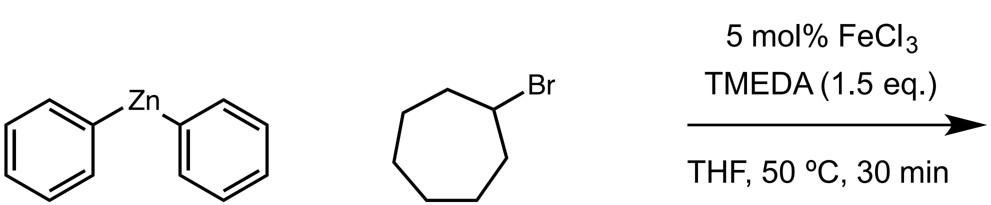
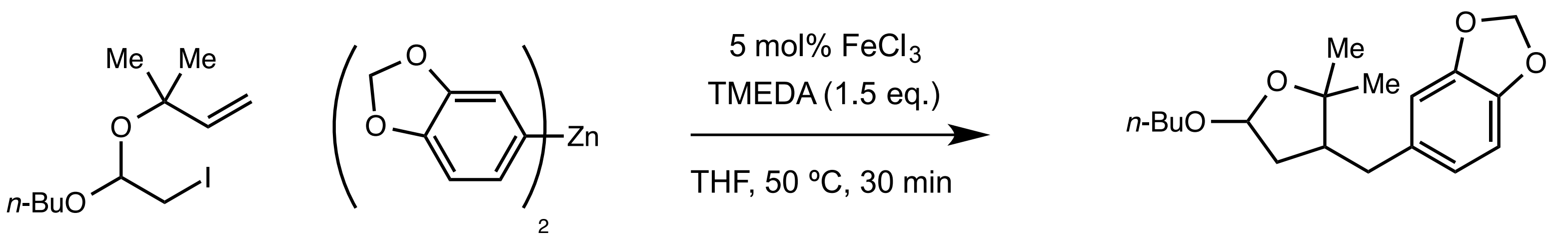



***96% yield***

■ Radical-based mechanisms are also proposed in this Negishi coupling




***86% yield***

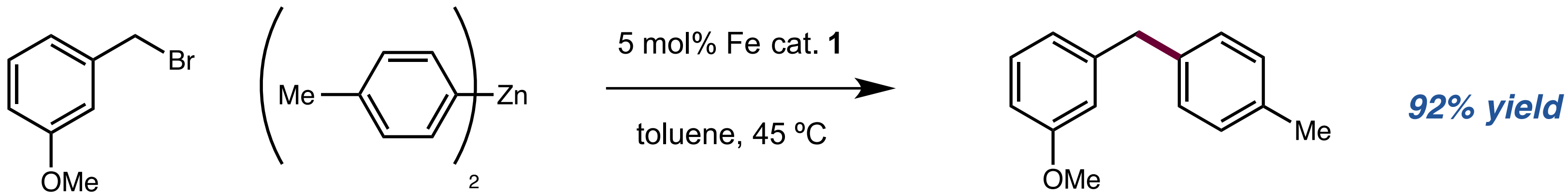
2:1 d.r.

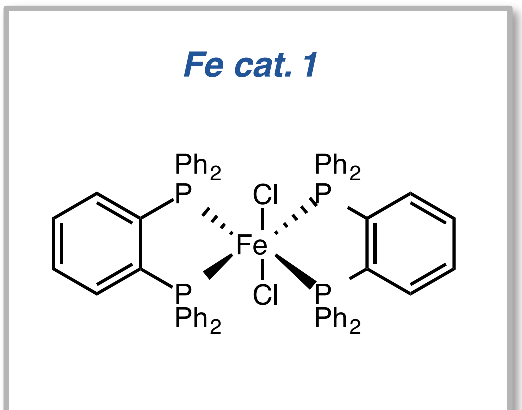

Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, *11*, 1794.

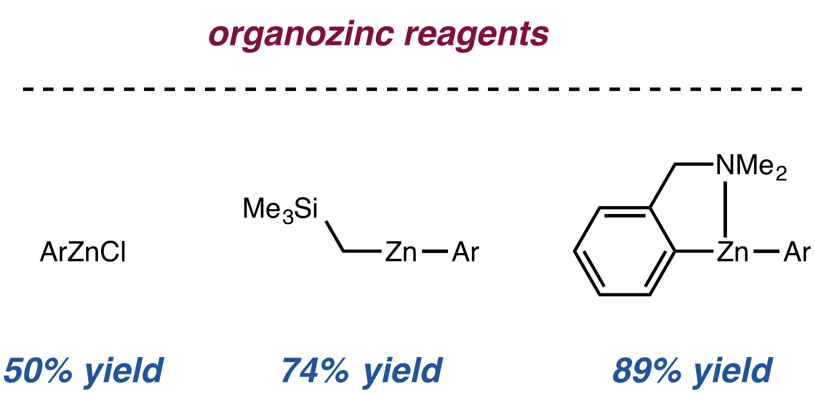
# *Iron-Catalyzed Negishi Cross-Coupling*

## Bedford demonstrated iron-phosphine complexes as suitable Negishi catalysts

- Benzyl halide and phosphate electrophiles couple with diarylzincs



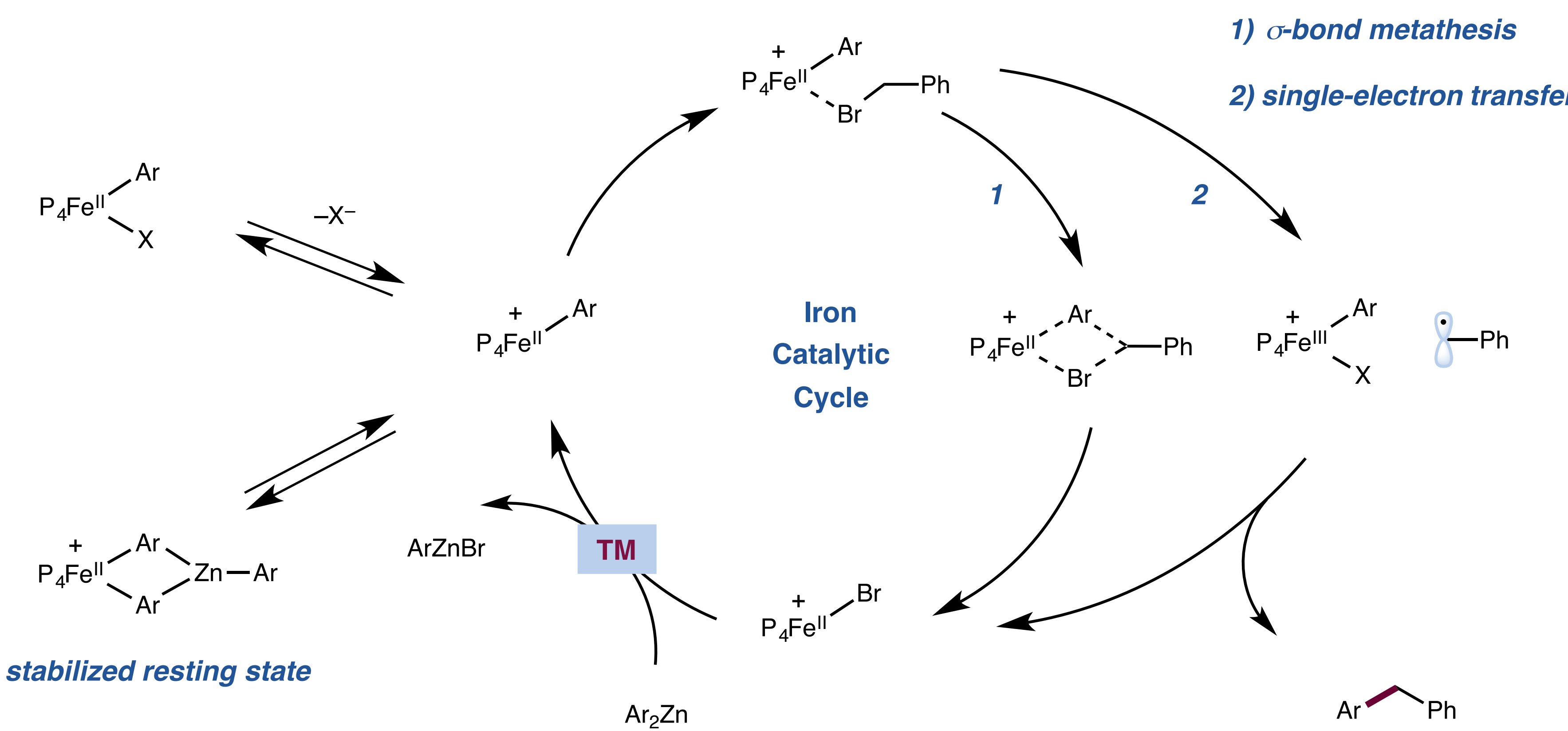




Bedford, R. B.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 600.

# *Iron-Catalyzed Negishi Cross-Coupling*

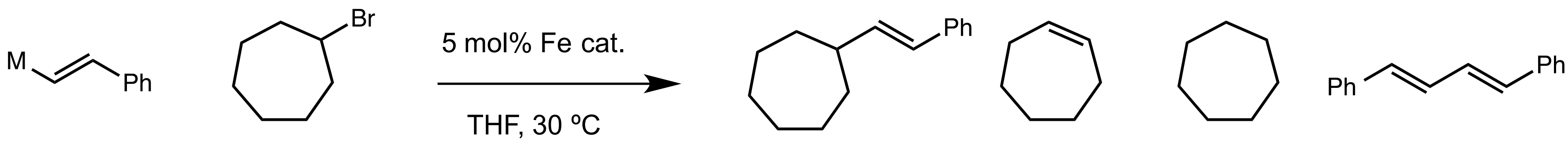
■ Bedford proposed a cationic Fe(II) catalytic cycle with two possible pathways




Bedford, R. B.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 600.

# *Iron-Catalyzed Negishi Cross-Coupling*

■ In 2009, Nakamura reported a stereospecific vinylation of alkyl halides with alkenyl zincs




**1a (M = ZnBr)** **2** **3** **4** **5** **6**

**1b (M = $ZnCH_2SiMe_3$)**

**1c (M = MgBr)**

| entry[a] | RM[b] | iron salt | additive (X equiv) | yield (%)[c] **3**[e] | **4** | **5** | RSM[d] (%)[c] **2** | **6** (mmol) |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | $FeCl_3$ | none | **8** | < 1 | 1 | 70 | 0.05 |
| 2 | **1b** | $FeCl_3$ | none | **25** | 4 | 17 | 0 | 0.12 |
| 3 | **1b** | $FeCl_3$ | TMEDA (1.5) | **56** | 4 | 13 | 0 | 0.11 |
| 4 | **1b** | $FeCl_3$ | TMEDA (3.0) | **91** | < 1 | 3 | 0 | 0.10 |
| 5 | **1b** | $FeCl_3$ | TMEDA (3.5) | **95** | < 1 | 3 | 0 | 0.08 |
| 6 | **1b** | $Fe(acac)_3$ | TMEDA (3.5) | **85** | 0 | 3 | 10 | 0.06 |
| 7 | **1b** | $FeCl_2$ | TMEDA (3.5) | **97** | < 1 | 3 | 0 | 0.05 |
| 8[f] | **1c** | $FeCl_3$ | TMEDA (3.5) | **35** | 12 | 4 | 35 | 0.02 |

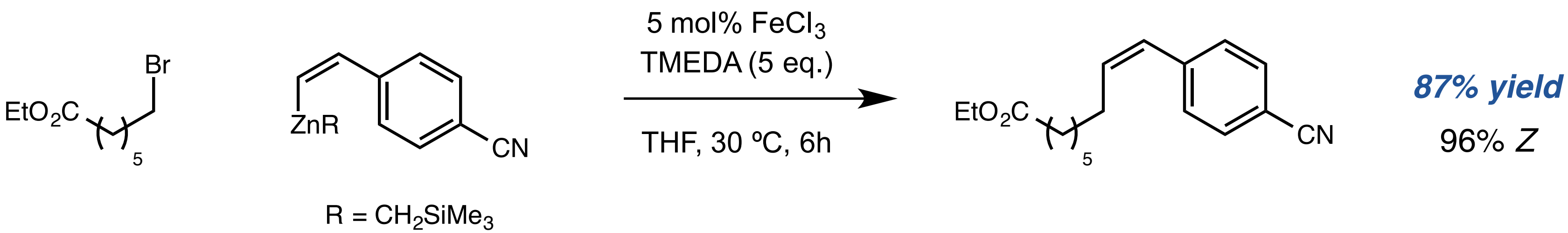
***excess TMEDA was necessary to ensure coordination of Fe in presence of Zn and Mg***

Hatakeyama, T.; Nakagawa, N.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4496.

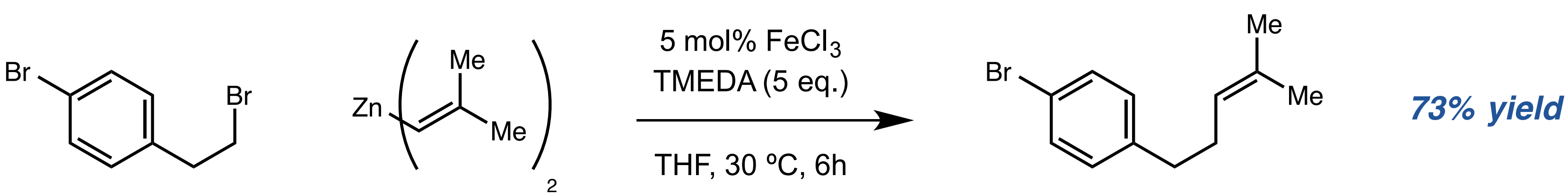
# *Iron-Catalyzed Negishi Cross-Coupling*

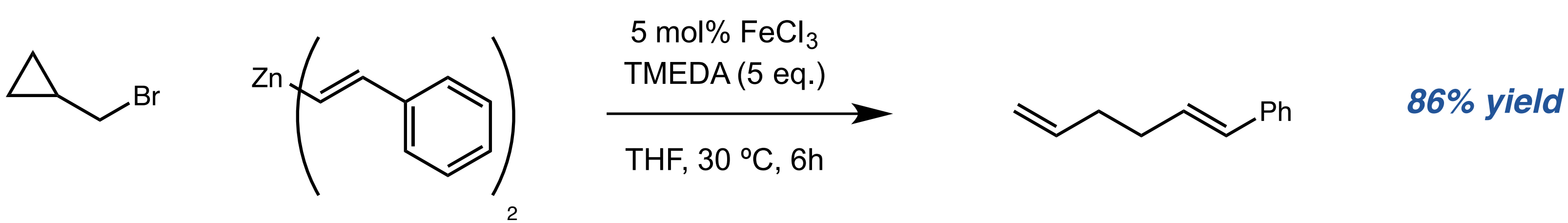
■ In 2009, Nakamura reported a stereospecific vinylation of alkyl halides with alkenyl zincs

■ Cross-coupling occurs with retention of olefin stereochemistry




■ Experiments support existence of radical intermediates

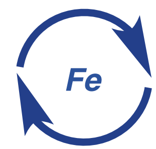




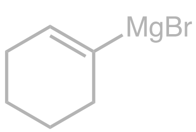
Hatakeyama, T.; Nakagawa, N.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4496.

# *Iron-Catalyzed Cross-Coupling*




## Kumada Coupling

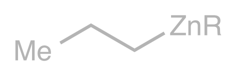
*Mg*




***Grignard reagents***

## Negishi Coupling

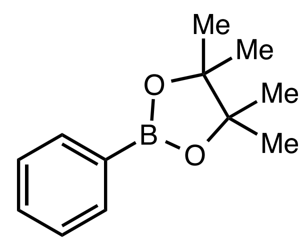
*Zn*




***organozincs***

## Suzuki Coupling

*B*




***organoboron***

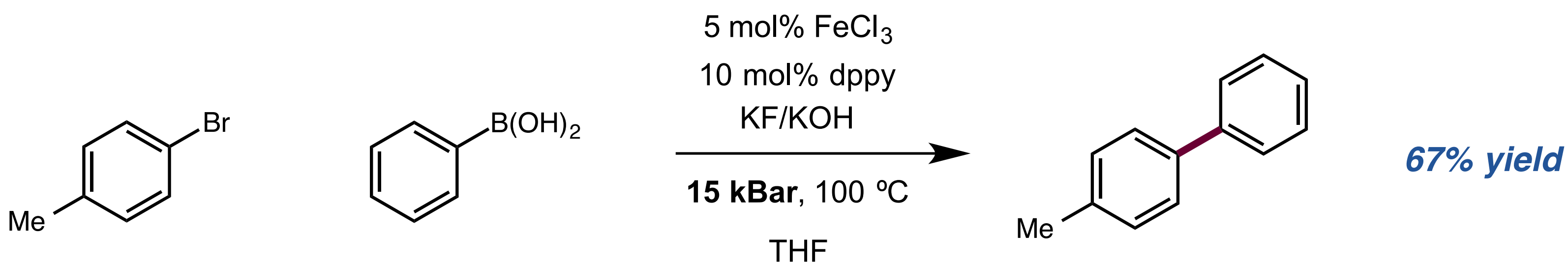
***"the iron-catalyzed Suzuki reaction...***
***...represents something of a 'holy grail' in coupling chemistry"***

***- R. B. Bedford and M. Nakamura, 2009***

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

## ■ First Fe-catalyzed Suzuki–Miyaura coupling was reported by Young in 2008

■ Elevated pressure (15 kBar) enables biaryl coupling




***high pressure is presumably assisting reduction of $FeCl_3$ down to low-valent active state***

Guo, Y.; Young, D. J.; Hor, T. S. A. *Tetrahedron Lett.* **2008**, *49*, 5620.

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■ Two additional publications proposed Fe-catalyzed Suzuki couplings to make biaryls (at ambient pressure)

Kylmala, T.; Valkonen, A.; Rissanen, K.; Xu., Y.; Franzen, R. *Tetrahedron Lett.* **2009**, *50*, 5692.

Bezier, D.; Darcel, C. *Adv. Synth. Catal.* **2010**, *352*, 1081.

***both publications were later retracted due to irreproducibility issues***

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

■ Joint study by Bedford and Nakamura determined trace Pd responsible for reactivity

- ■ Biaryl coupling could not be reproduced with a range of iron catalysts
- ■ Coupling was observed with ppb levels of Pd, therefore Pd contamination likely

***"the iron-catalyzed Suzuki biaryl coupling reaction appears to be, for the moment at least, out of reach"***

Bedford, R. B.; Nakamura, M.; Gower, N. J.; Haddow, M. F.; Hall, M. A.; Huwe, M.; Hashimoto, T.; Okopie, R. A. *Tetrahedron Lett.* **2009**, *50*, 6110.

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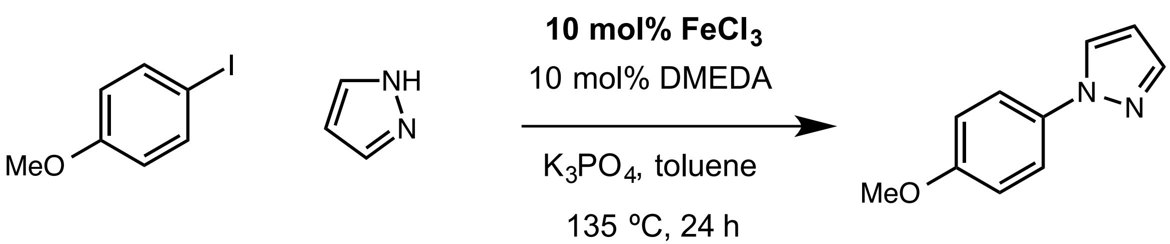
■ Buchwald and Bolm made similar observations in the Fe-catalyzed C–N coupling

- ■ Commercial Fe catalysts contained trace Cu, resulting in false activity

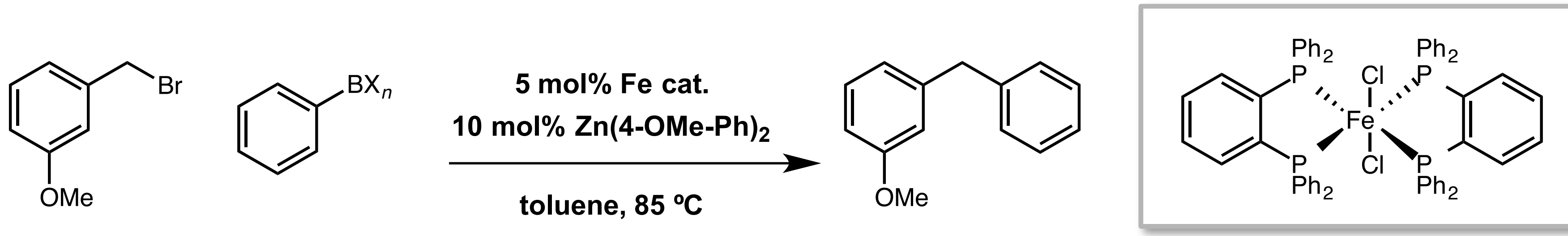


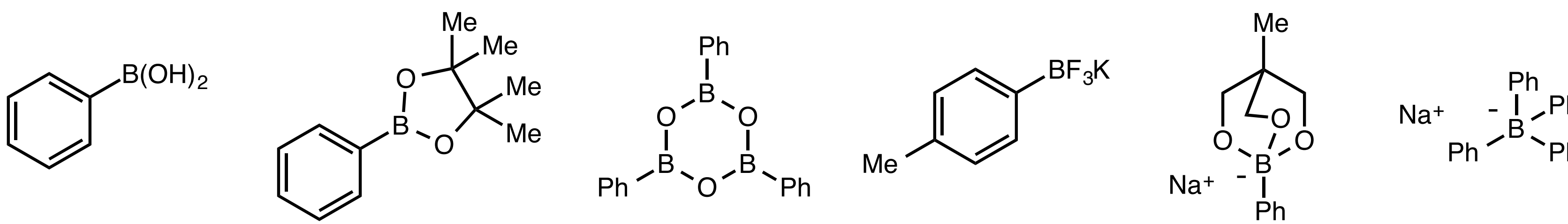

| $FeCl_3$ | Yield |
|---|---|
| **> 98% (Merck)** | **87%** |
| **> 99.99% (Aldrich)** | **9%** |
| **no Fe, 5 ppm $Cu_2O$** | **77%** |

Buchwald, S. L.; Bolm, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5586.

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

■ Bedford employed a mixed Fe–Zn catalytic system to access organoboron nucleophiles




| | | | | | |
|---|---|---|---|---|---|
| *0% yield* | *0% yield* | *0% yield* | *0% yield* | *0% yield* | *96% yield* |

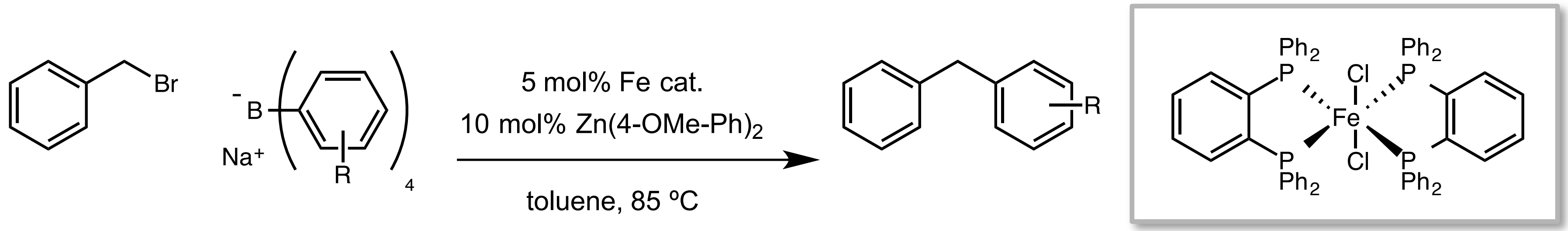
***no incorporation of Zn aryl groups into product***

***diaryl zinc is likely consumed during reductive activation of Fe catalyst***

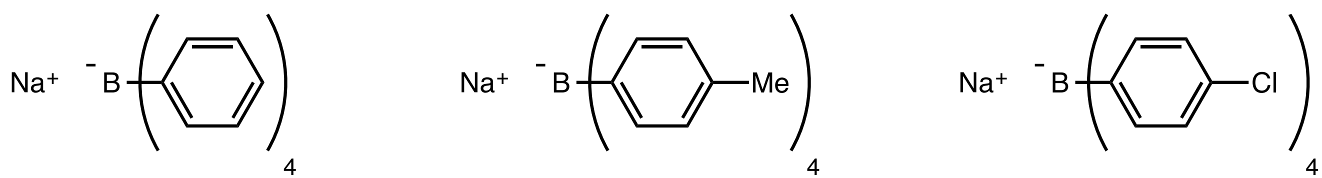
Bedford, R. B.; Hall, M. A.; Hodges, G. R.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 6430.

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

■ Bedford employed a mixed Fe–Zn catalytic system to access organoboron nucleophiles




***Limited nucleophile scope:***




*91% yield* *96% yield* *trace yield*

***Mechanistic Considerations:***

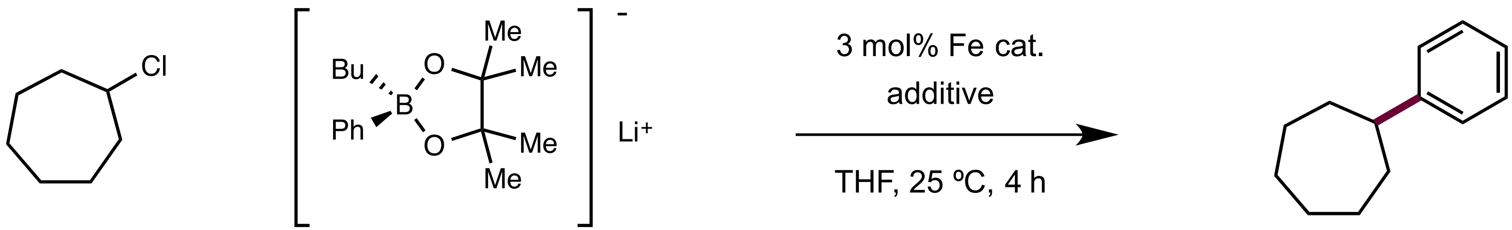
***Zn co-catalyst likely plays a role in boron transmetallation with Fe center via arylzinc intermediate***

***Bedford proposes an Fe(I) oxidation state for the active catalyst***

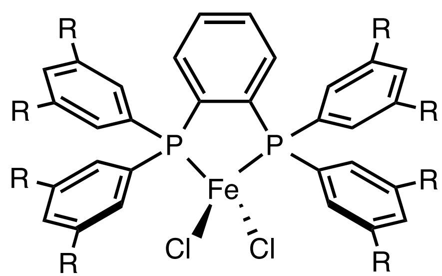
Bedford, R. B.; Hall, M. A.; Hodges, G. R.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 6430.

# Iron-Catalyzed Suzuki–Miyaura Cross-Coupling

## Nakamura reported Suzuki coupling with aryl boronates using novel diphosphine ligands




***prepared in situ from boronate ester and R–Li***




**1** (R = *t*-Bu)
**2** (R = $SiMe_3$)

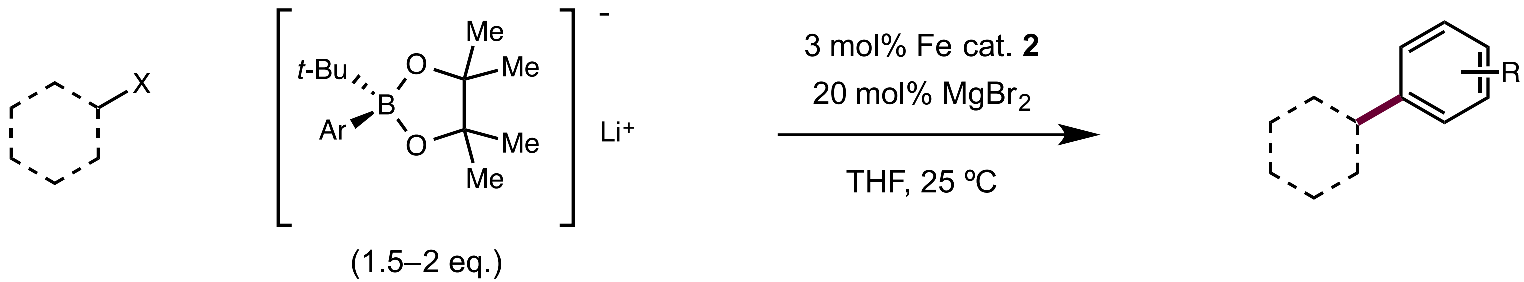
| entry[a] | catalyst (3 mol %) | additive (mol %) | yield (%)[b] | recovery (%)[b] |
|---|---|---|---|---|
| 1 | $FeCl_3$ | TMEDA (200) | 0 | >99 |
| 2 | $FeCl_3$ | TMEDA (200) + $MgBr_2$ (20) | 0 | >99 |
| 3 | $FeCl_2(dppbz)_2$ | none | 0 | >98 |
| 4 | $FeCl_2(dppbz)_2$ | $MgBr_2$ (20) | 14 | 83 |
| 5 | complex **1** | $MgBr_2$ (20) | **93** | 0 |
| 6 | complex **2** | $MgBr_2$ (20) | **91** | 0 |
| 7 | complex **2** | none | 0 | >99 |

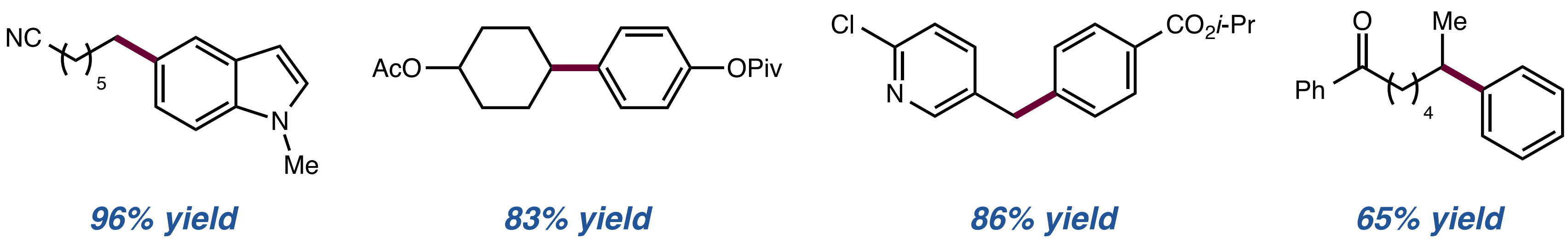
***bulky diphosphine ligand prevents formation of coordinatively saturated octahedral Fe complex***

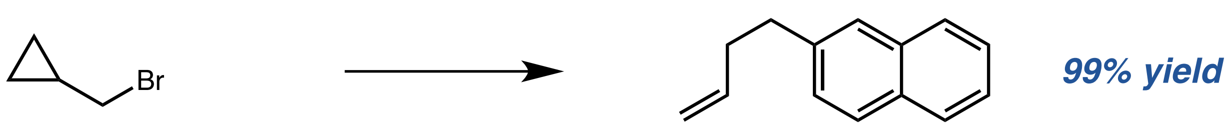
Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674.

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

■ Nakamura reported Suzuki coupling with aryl boronates using novel diphosphine ligands



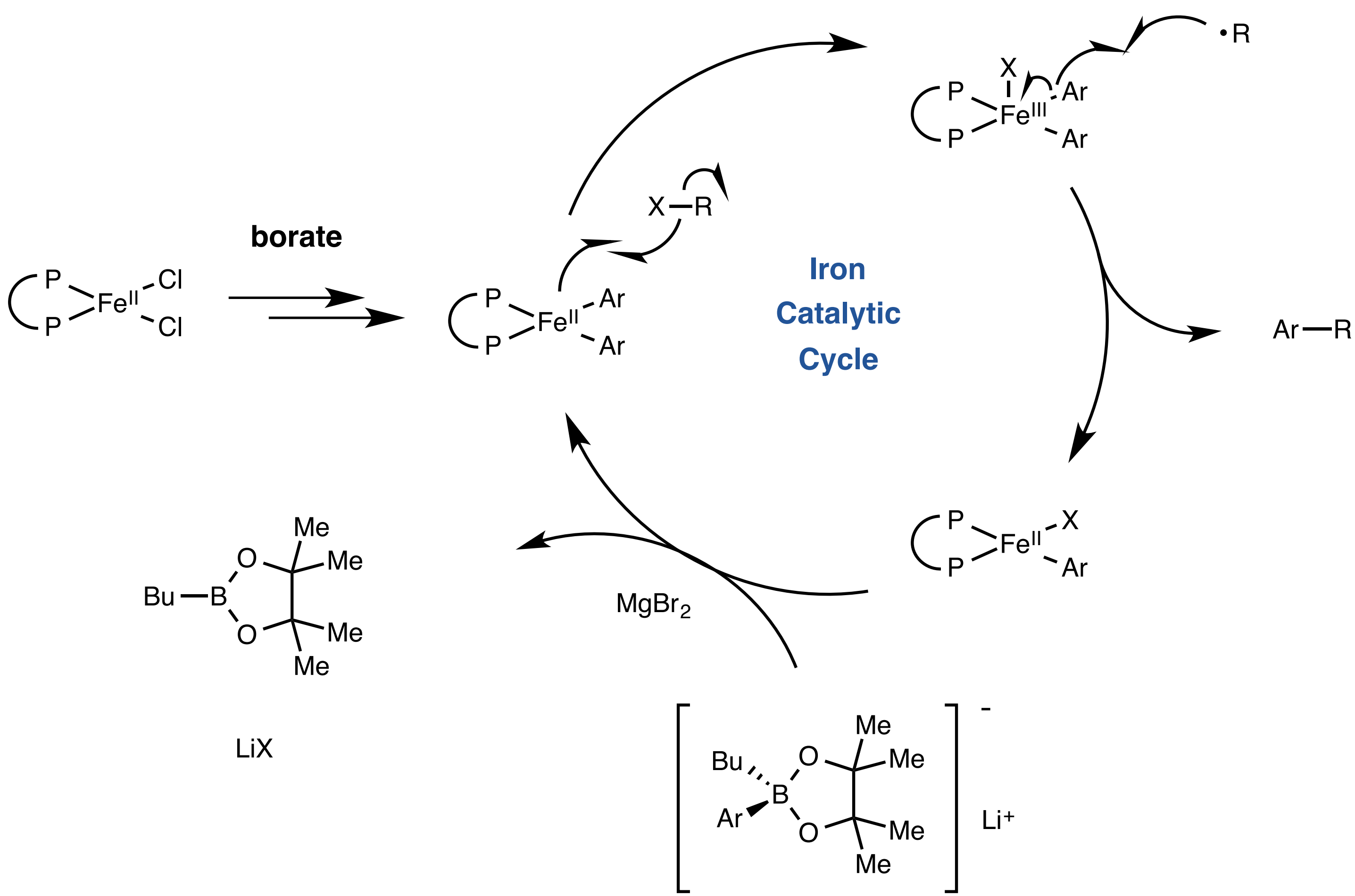





Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674.

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

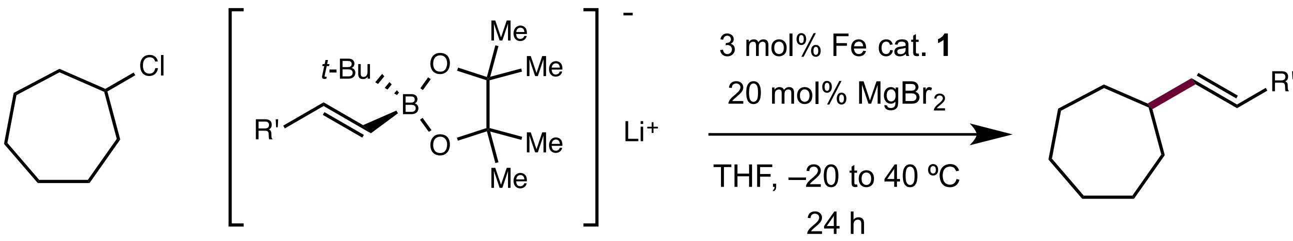
## ■ Nakamura proposes an Fe(II)/(III) cycle



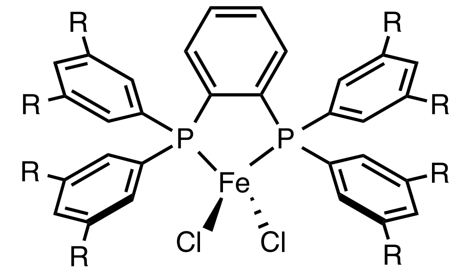

Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674.

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

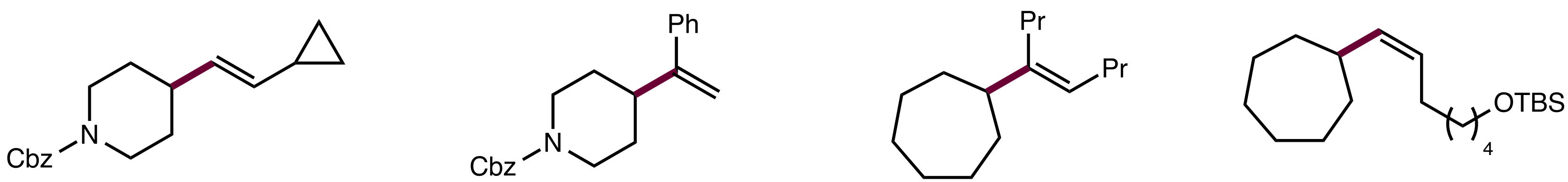
## ■ Nakamura extended this catalytic platform to vinylation




***prepared in situ from boronate ester and t-Bu–Li***




**1** (R = *t*-Bu)
**2** (R = $SiMe_3$)




***85% yield*** >99% *E*

***77% yield***

***58% yield*** >99% *E*

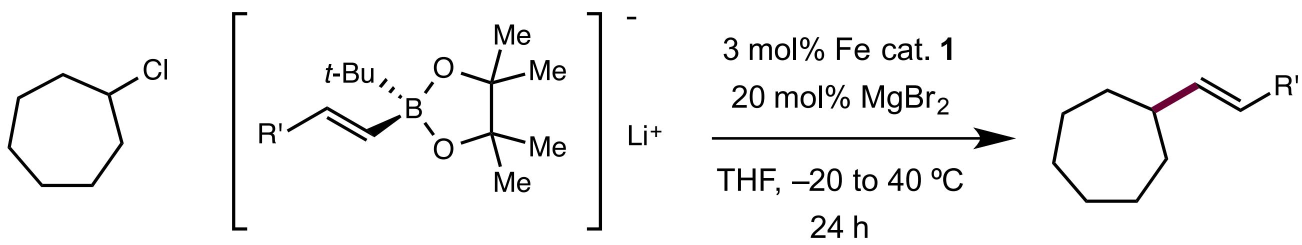
***93% yield*** >99% *Z*

***vinylation proceeds with retention of olefin stereochemistry***

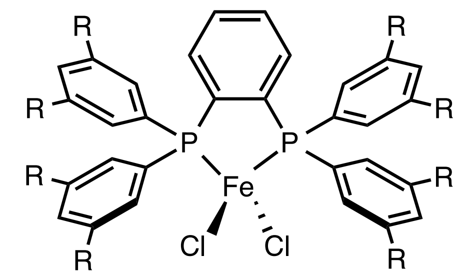

Hashimoto, T.; Hatakeyama, T.; Nakamura, M. *J. Org. Chem.* **2012**, *77*, 1168.

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

## ■ Nakamura extended this catalytic platform to vinylation




***prepared in situ from boronate ester and t-Bu–Li***




**1** (R = *t*-Bu)
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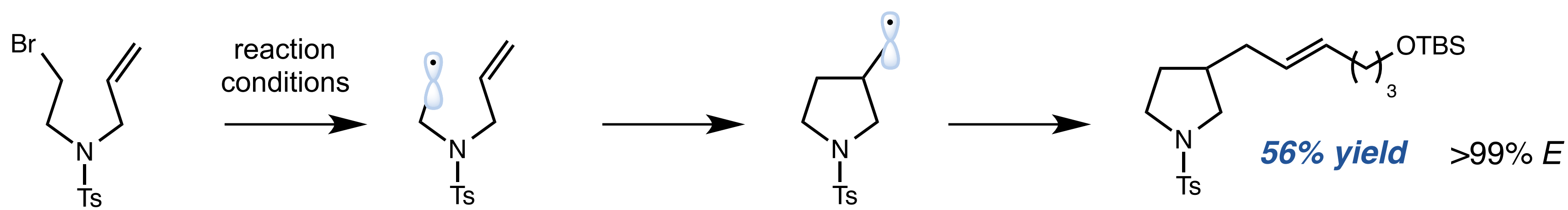
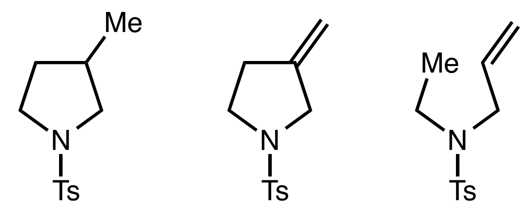



***Fe(II) abstracts Br• resulting in 5-exo cyclization and coupling***

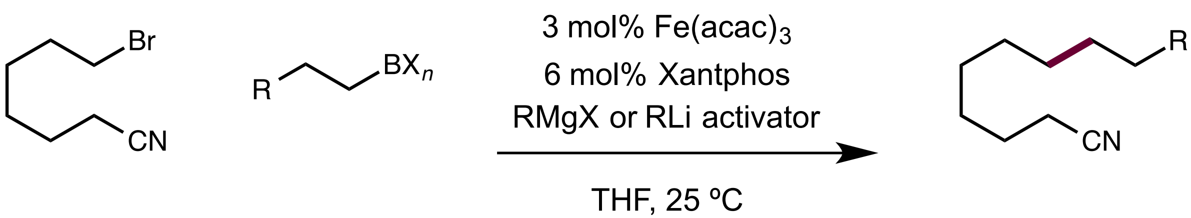


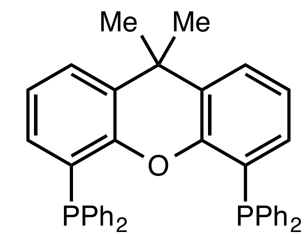

**25%** **3%** **10%**

Hashimoto, T.; Hatakeyama, T.; Nakamura, M. *J. Org. Chem.* **2012**, *77*, 1168.

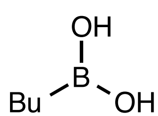
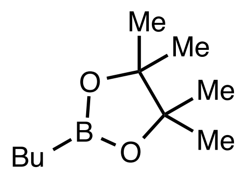
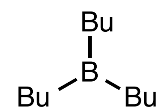
# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

■ In 2012, Nakamura reported the first iron-catalyzed *$sp^3$–$sp^3$* Suzuki-Miyaura cross-coupling




***Xantphos***

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Nucleophile*** |  |  |  | | | | |
| ***Activator*** | both RMgX and RLi | | *n*-BuMgCl | *n*-BuLi | *t*-BuMgCl | MeMgBr | *i*-PrMgCl |
| | ***0% yield*** | ***0% yield*** | ***85% yield*** | ***0% yield*** | ***0% yield*** | ***8% yield**** | ***82% yield*** |

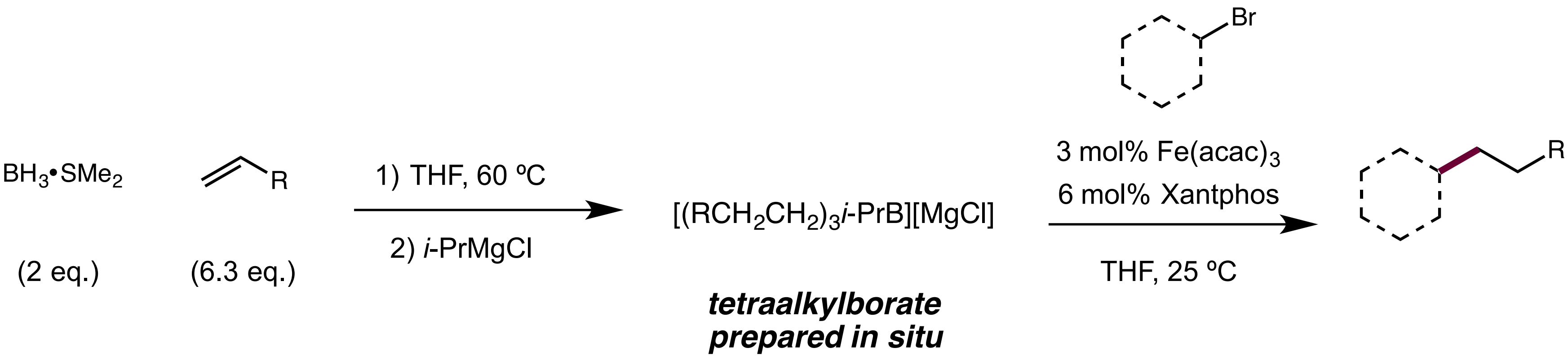
****competing Me group transmetallation = 73% methylated product***

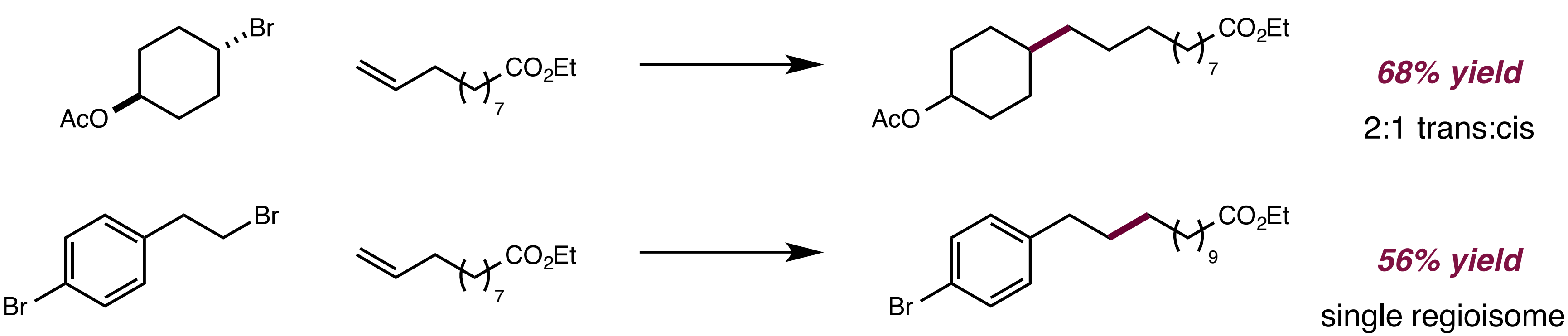
***rate of alkyl group transfer in transmetallation: Me > 1° alkyl > 2° alkyl***


Hatakeyama, T.; Hashimoto, T.; Kathriarachchi, K. K. A. D. S.; Zenmyo, T.; Seike, H.; Nakamura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 8834.

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

■ To expand nucleophile scope, Nakamura prepared tetraalkylborates in situ via hydroboration



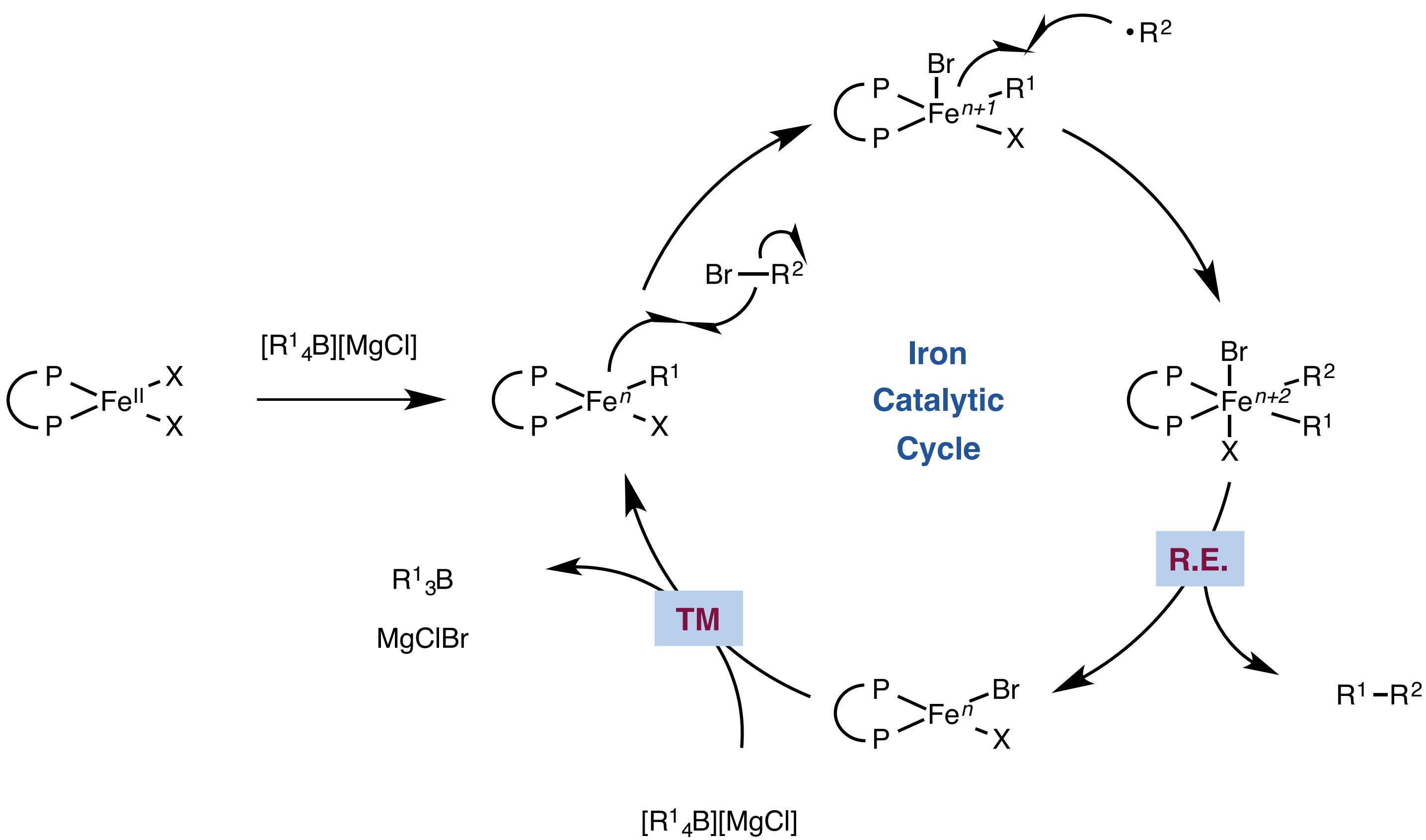




***a radical mechanism is proposed***

Hatakeyama, T.; Hashimoto, T.; Kathriarachchi, K. K. A. D. S.; Zenmyo, T.; Seike, H.; Nakamura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 8834.

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

■ Nakamura proposes radical-based mechanism

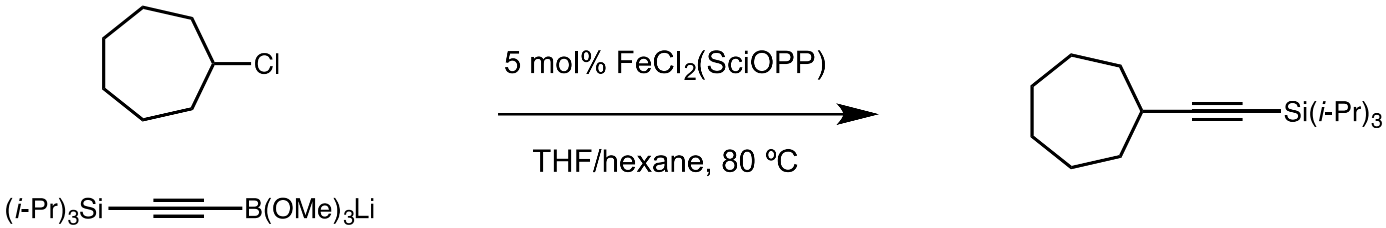



***n* = +2, +1, or lower oxidation state**

Hatakeyama, T.; Hashimoto, T.; Kathriarachchi, K. K. A. D. S.; Zenmyo, T.; Seike, H.; Nakamura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 8834.

# *Iron-Catalyzed Suzuki–Miyaura Cross-Coupling*

## ■ Nakamura has also reported Fe-catalyzed Suzuki alkynylation




***80% yield***

Nakagawa, N.; Hatakeyama, T.; Nakamura, M. *Chem. Lett.* **2015**, *44*, 486.

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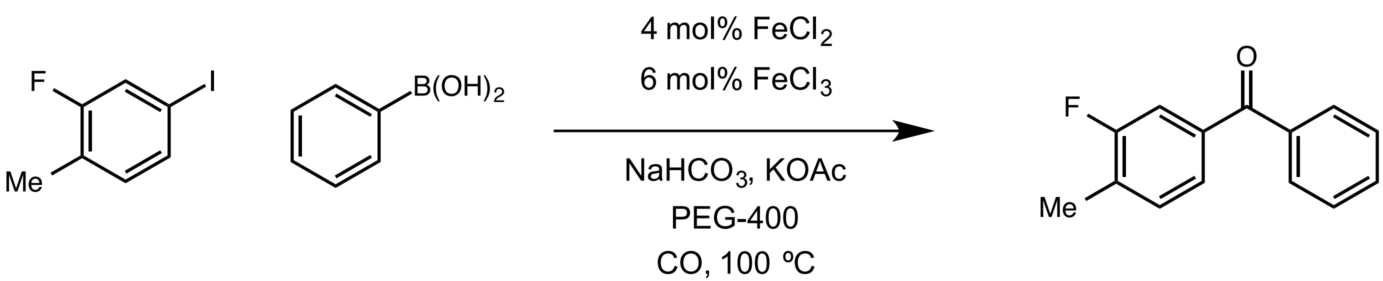
## ■ Han reported an Fe-catalyzed carbonylative Suzuki coupling to make bisaryl ketones

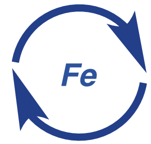



***82% yield***

***$Fe_m(CO)_n$ generated in situ is active catalyst***

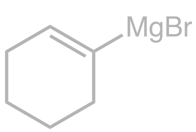
Zhong, Y.; Han, W. *Chem. Commun.* **2014**, *50*, 3874.

*Iron-Catalyzed Cross-Coupling*




Kumada Coupling

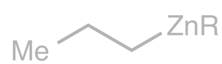
*Mg*




***Grignard reagents***

Negishi Coupling

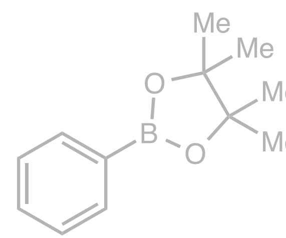
*Zn*




***organozincs***

Suzuki Coupling

*B*

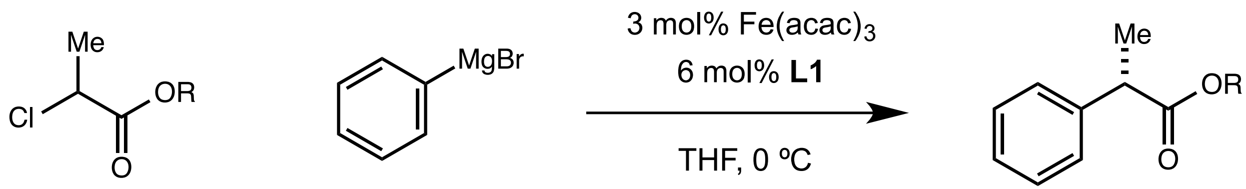



***organoboron***

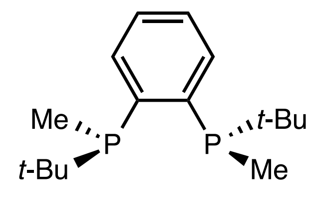
***What about asymmetric catalysis?***

# *Asymmetric Iron-Catalyzed Cross-Coupling*

■ In 2015, Nakamura reported the first asymmetric Fe-catalyzed cross-coupling reaction

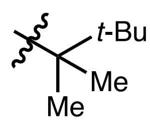



***racemic*** 2 eq.




**L1** (*R*,*R*)-BenzP*

| | |
|---|---|
| **R = *t*-Bu** | **91% yield, 87:13 er** |
| **R = *i*-Pr** | **75% yield, 83:17 er** |
| **R = Et** | **40% yield, 82:18 er** |
| **R = theptyl** | **82% yield, 90:10 er** |



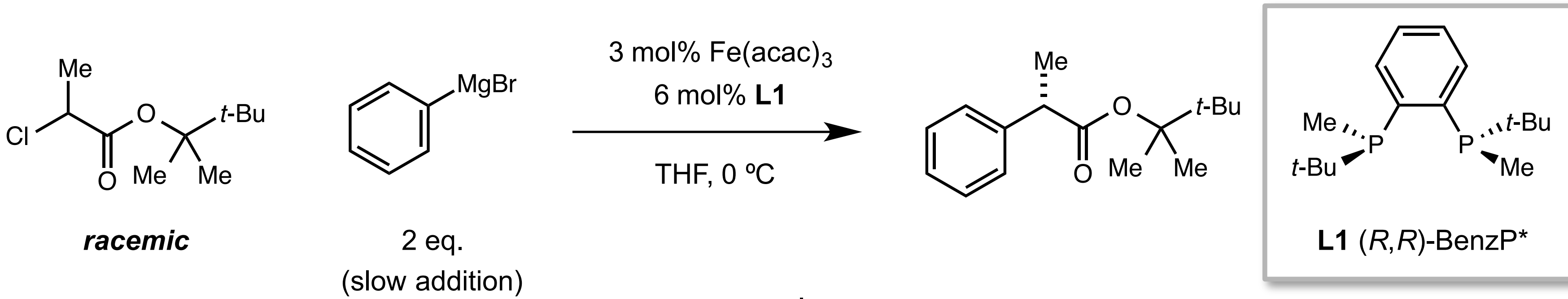

***slow addition of Grignard and avoiding strongly coordinating solvents (DMPU, NMP) improved er***

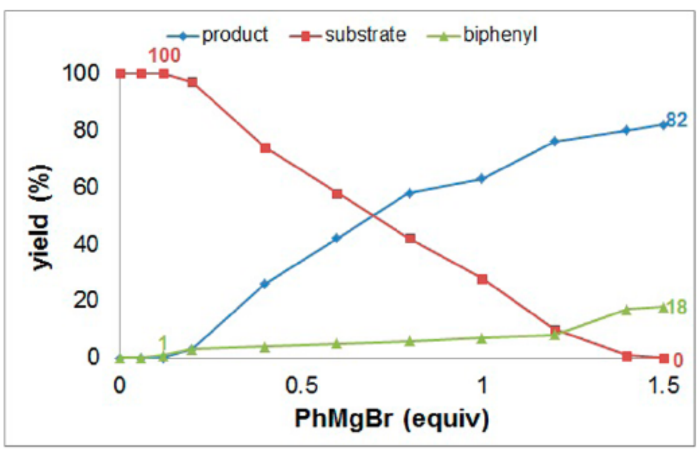
***this helped to ensure the Fe catalyst was constantly ligated to the chiral ligand***

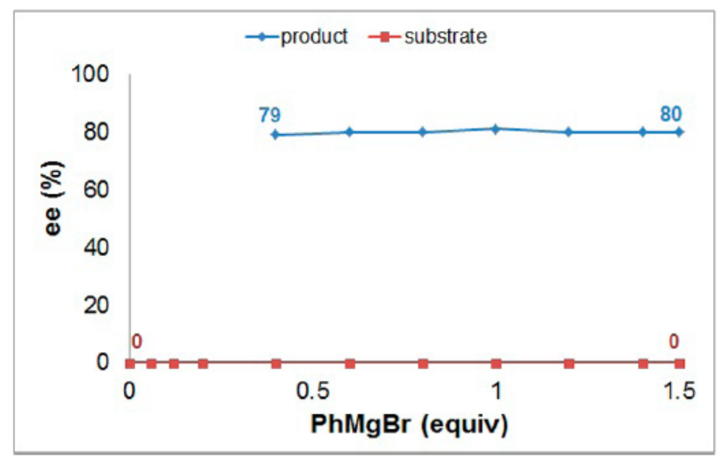

Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128.

# *Asymmetric Iron-Catalyzed Cross-Coupling*

■ In 2015, Nakamura reported the first asymmetric Fe-catalyzed cross-coupling reaction




***no coupling until 0.12 eq. PhMgBr has been added***

***PhMgBr reduces Fe catalyst to Fe(II) state***

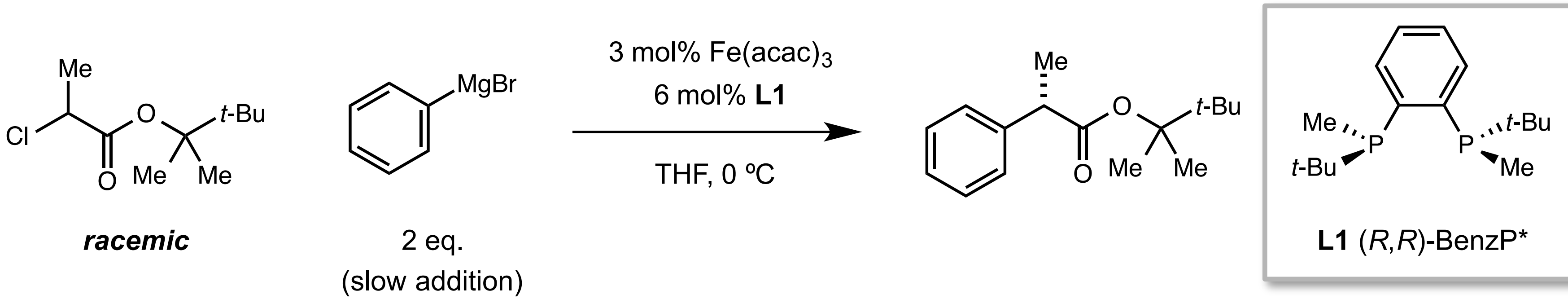
***no kinetic resolution of substrate***

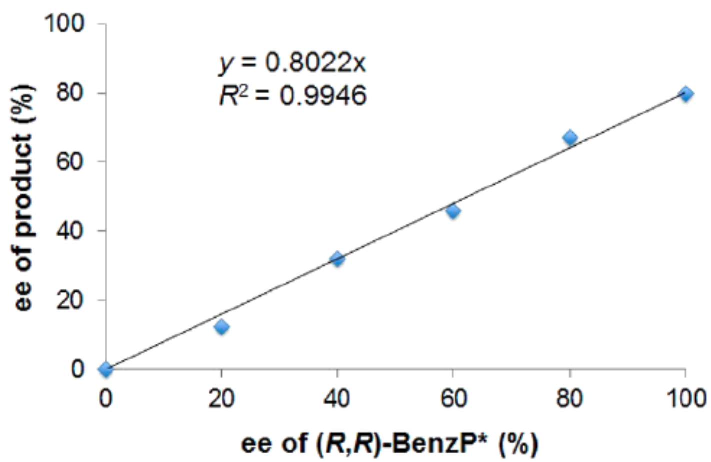
***C–C bond formation is selectivity-determining step***


Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128.

# *Asymmetric Iron-Catalyzed Cross-Coupling*

■ In 2015, Nakamura reported the first asymmetric Fe-catalyzed cross-coupling reaction



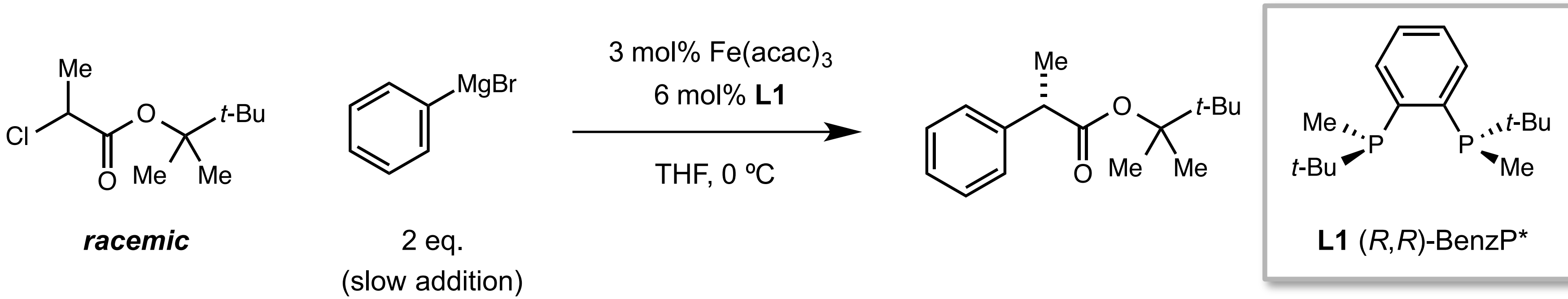

***ee of product directly proportional to ee of chiral ligand***

***enantioselectivity determined by chiral phosphine–iron complex***

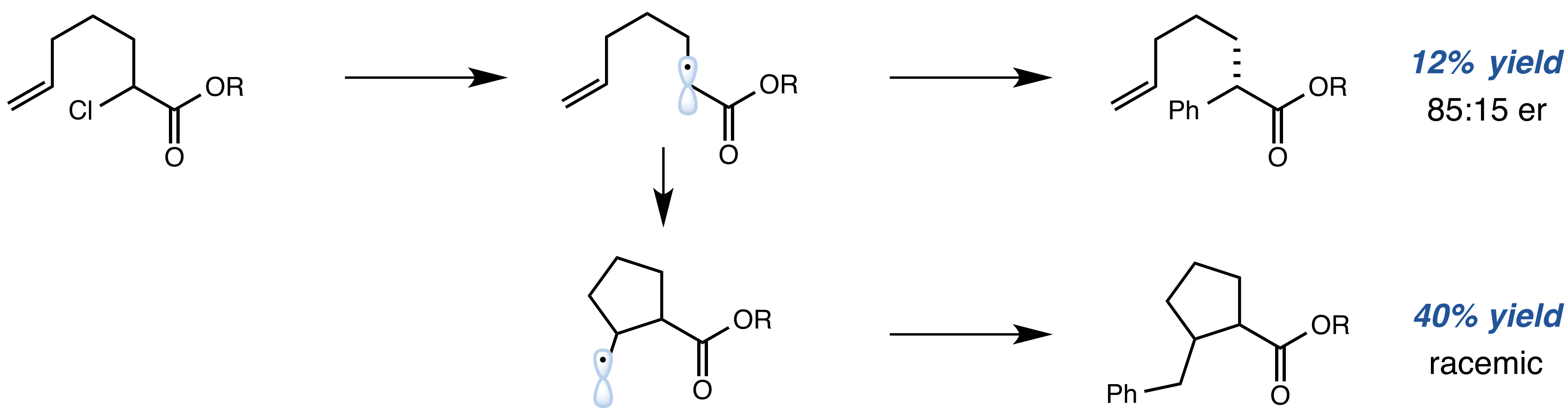
Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128.

# *Asymmetric Iron-Catalyzed Cross-Coupling*

■ In 2015, Nakamura reported the first asymmetric Fe-catalyzed cross-coupling reaction



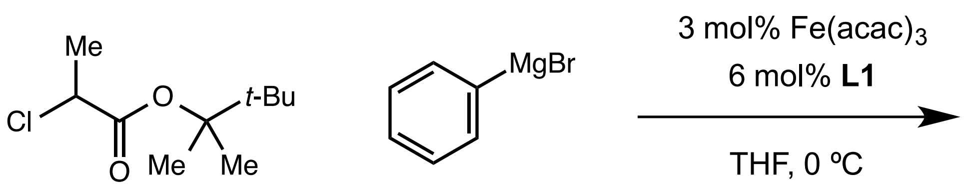

***Radical probe experiment:***




Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128.

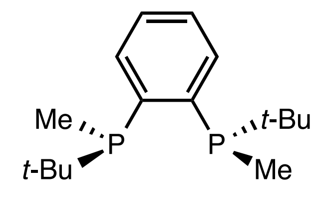
# *Asymmetric Iron-Catalyzed Cross-Coupling*

■ In 2015, Nakamura reported the first asymmetric Fe-catalyzed cross-coupling reaction

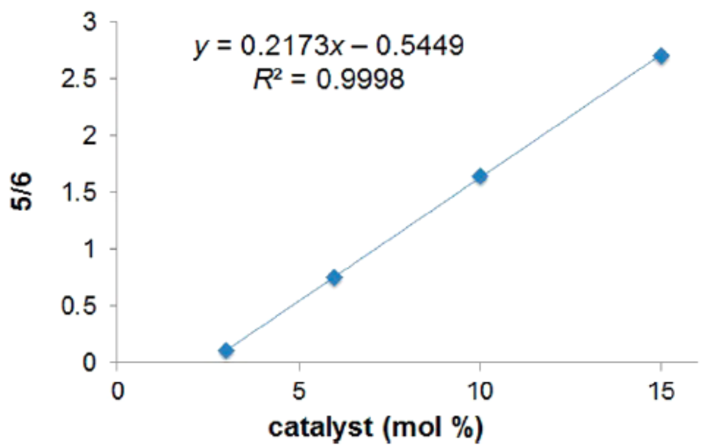


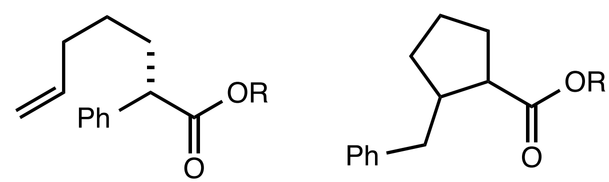

***racemic***

2 eq.
(slow addition)




**L1** (*R*,*R*)-BenzP*




**5** **6**

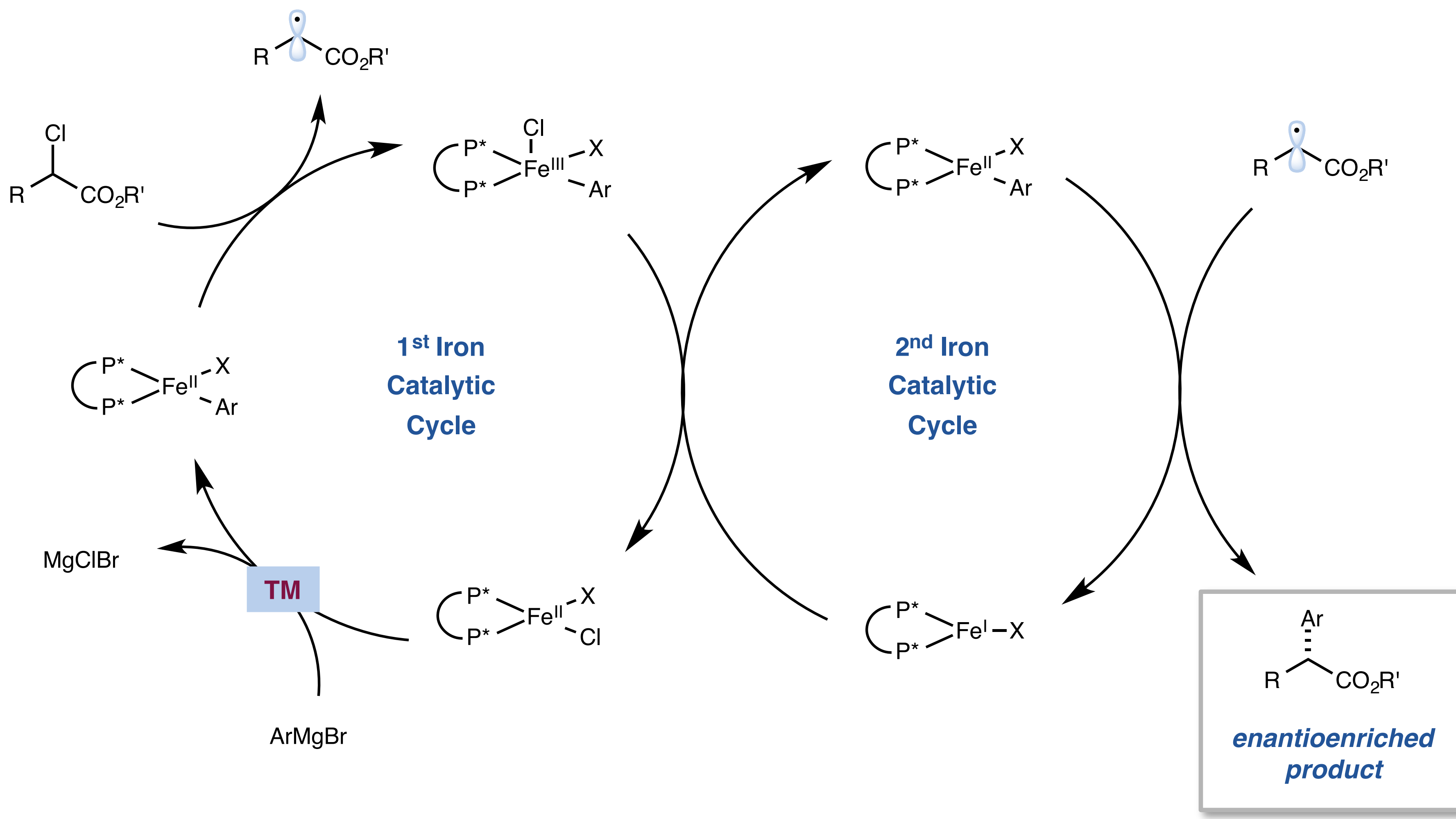
***1st order relationship between ratio of 5/6 and catalyst loading***

***alkyl radical intermediate escapes solvent cage, cyclizes, and then undergoes arylation with 2nd iron catalyst***

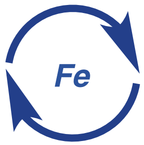
Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128.

# *Asymmetric Iron-Catalyzed Cross-Coupling*

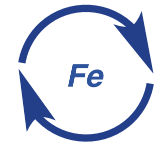
## ■ Nakamura proposes a bimetallic out-of-cage mechanism




Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128.

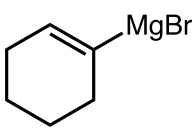



# *Iron-Catalyzed Cross-Coupling*




## Kumada Coupling

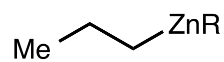
*Mg*




***Grignard reagents***

## Negishi Coupling

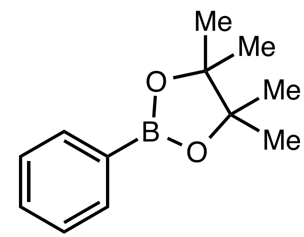
*Zn*




***organozincs***

## Suzuki Coupling

*B*

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## ***Useful Reviews***


Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500.

Czaplik, W. M.; Mayer, M.; Cvengros, J.; von Wangelin, A. J. *ChemSusChem* **2009**, *2*, 396.

Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

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Bedford, R. B. *Acc. Chem. Res.* **2015**, *48*, 1485.

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