

Recent advances in iron-catalyzed cross-coupling reactions

CH-707: Frontiers in Chemical Synthesis -
Towards Sustainable Chemistry

11.05.2020

Alexandre Leclair

Important literature

Books:

M. Nakamura *et al.*, in *Org. React.*, American Cancer Society, **2014**, pp. 1–210.

E. Bauer, Ed. , *Iron Catalysis II*, Springer International Publishing, Cham, **2015**.

Reviews:

I. Bauer and H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387

T. L. Mako and J. A. Byers, *Inorg. Chem. Front.*, **2016**, *3*, 766

M. L. Neidig *et al.*, *J. Am. Chem. Soc.* **2018**, *140*, 11872–11883 / *Acc. Chem. Res.* **2019**, *52*, 140–150

**CHEMICAL
REVIEWS**

Iron Catalysis in Organic Synthesis

Ingmar Bauer and Hans-Joachim Knölker*

Recent advances in iron-catalysed cross coupling reactions and their mechanistic underpinning

T. L. Mako and J. A. Byers*

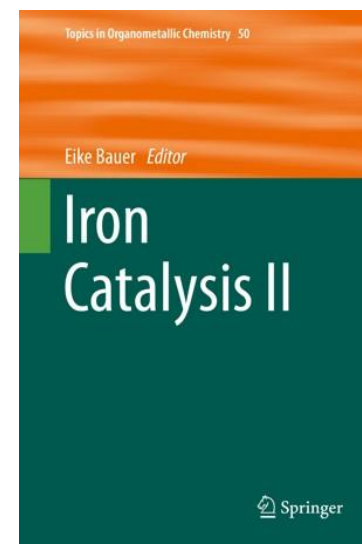


Table of contents

I. Introduction

II. Preliminary works on iron-catalyzed cross-coupling

III. Recent progress for classical cross-coupling reactions

→ Focus on mechanism investigations

IV. Conclusion and outlooks

I. Introduction

II. Preliminary works on iron-catalyzed cross-coupling

III. Recent progress for classical cross-coupling reactions

→ Focus on mechanism investigations

IV. Conclusion and outlooks

Introduction

25 Mn	26 Fe	27 Co	28 Ni
43 Tc	44 Ru	45 Rh	46 Pd



Fe
[Ar] 3d⁶ 4s²
Transition metal



Stable isotopes: ⁵⁴Fe, ⁵⁶Fe, ⁵⁷Fe, ⁵⁸Fe

Oxidation states: -II, -I, **0**, +I, **+II**, **+III**, +IV, +V, +VI

FeCl₂, FeCl₃, Fe(acac)₃

Readily available: 4th more abundant element in the Earth's crust

Cheap: 0.081 €/kg

Relatively non-toxic:

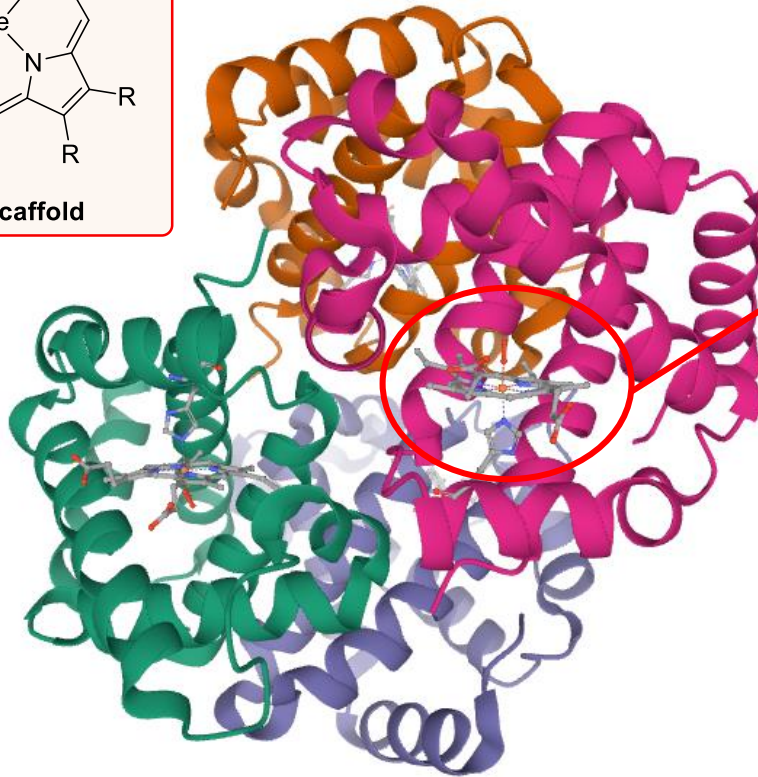
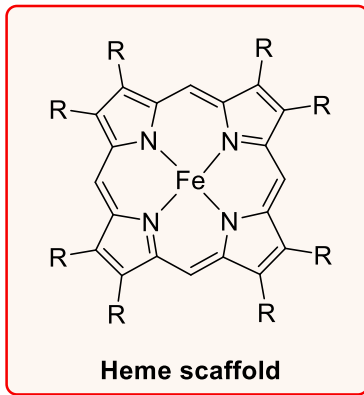
Acceptable level in drugs → 1300 ppm Vs ≤10 ppm for most transition metals

A. Fürstner *et al.*, *ACS Cent. Sci.* **2016**, *2*, 778–789

European Medicines Agency, Guideline on the Specification: Limits for Residues of Metal Catalysts or Metal Reagents, EMEA/CHMP/SWP/4446/2000, London, February 21, 2008.

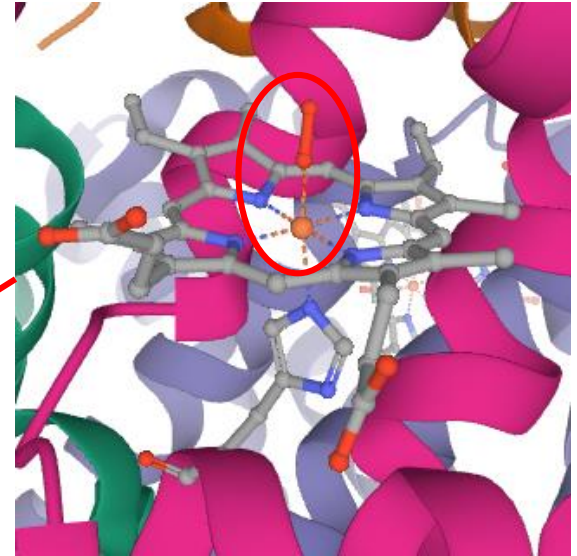
Introduction

In biology: Transport of oxygen in vertebrates



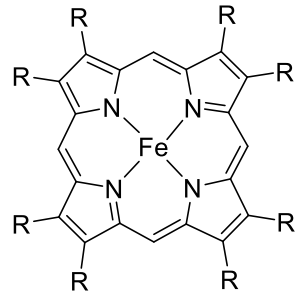
Hemoglobin

Oxygen complexation

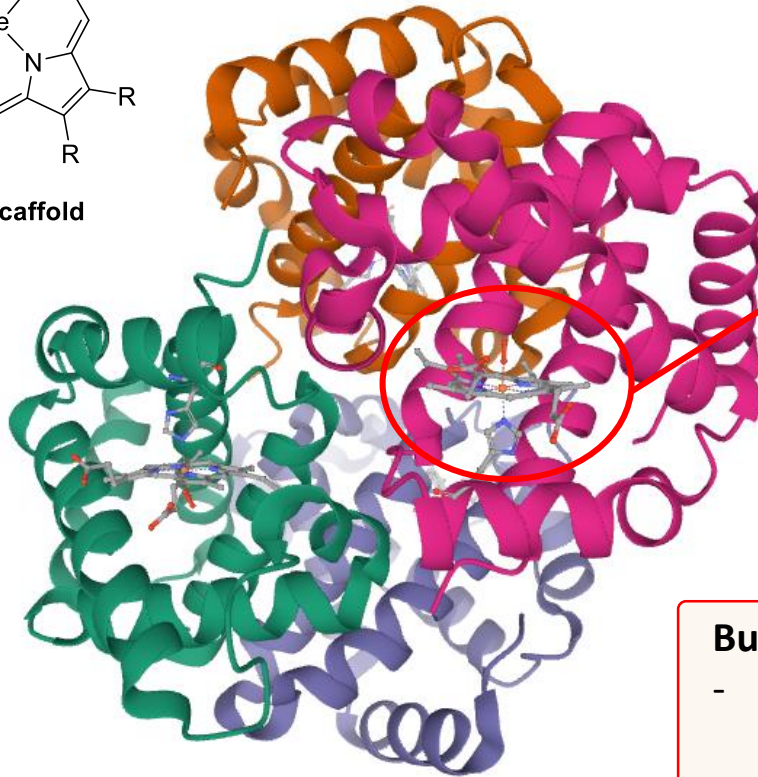


Introduction

In biology: Transport of oxygen in vertebrates

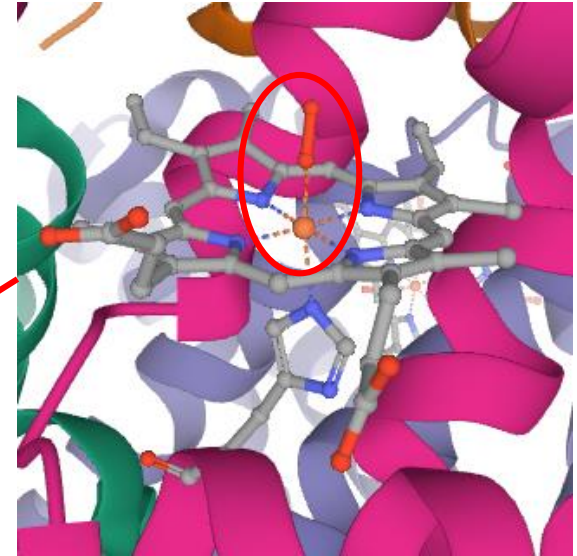


Heme scaffold



Hemoglobin

Oxygen complexation



But also:

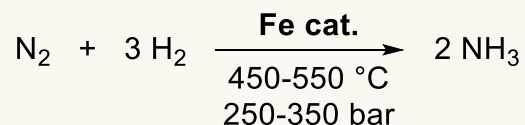
- For the transfer of electrons in the cellular respiration (**Fe-S proteins**)
- For the immune system (**lactoferrin**)
- ...

Introduction

Applications in industrial productions:

- Production of ammonia (**Haber-Bosch process**):

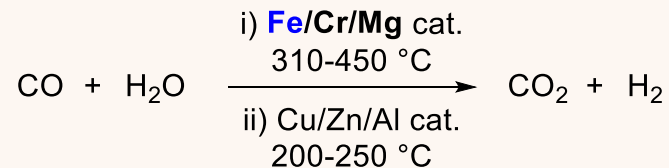
→ Main source of ammonia for nitrogen fertilizer



- Production of alkanes (**Fischer-Tropsch process**):



- Production of hydrogen gas (**Water-gas shift reaction**):

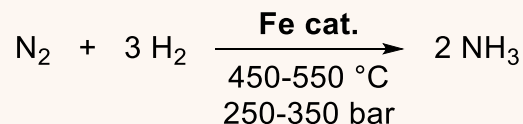


Introduction

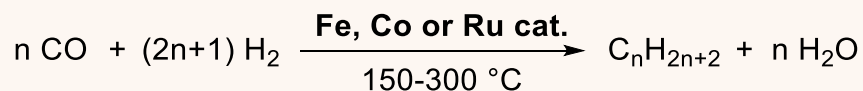
Applications in industrial productions:

- Production of ammonia (**Haber-Bosch process**):

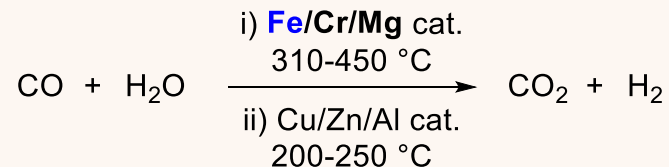
→ Main source of ammonia for nitrogen fertilizer



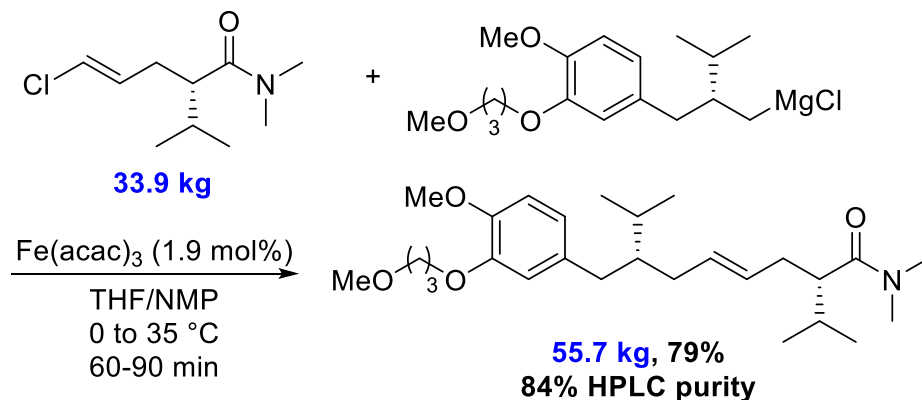
- Production of alkanes (**Fischer-Tropsch process**):



- Production of hydrogen gas (**Water-gas shift reaction**):



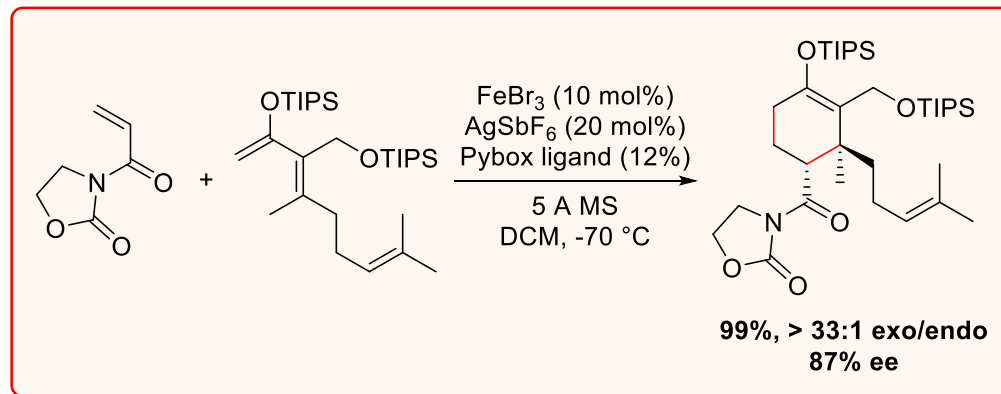
- Current investigations in cross-couplings:



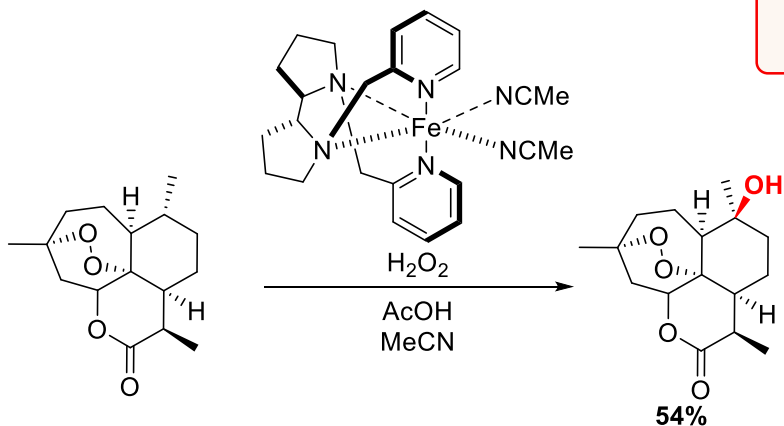
Introduction

Broad range of applications:

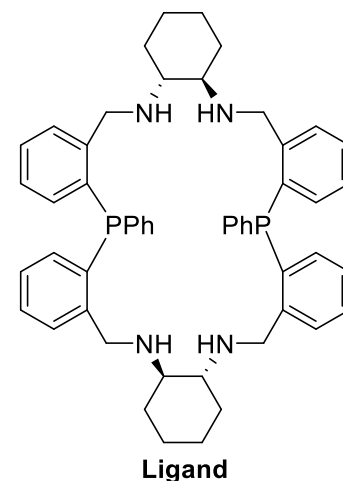
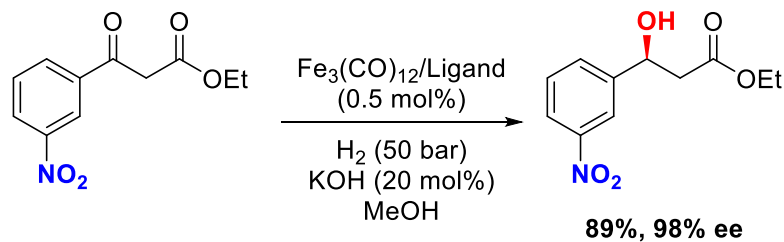
As Lewis acid: Diels-Alder, Friedel-Crafts, ...



As catalyst in oxidation: C-H functionalization



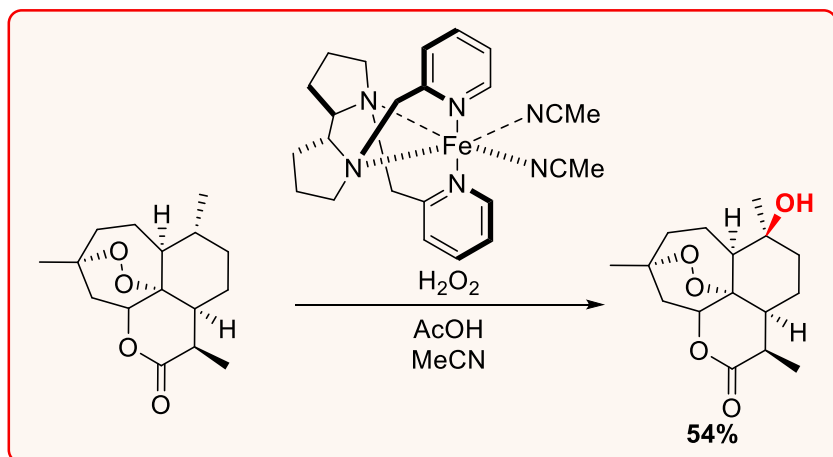
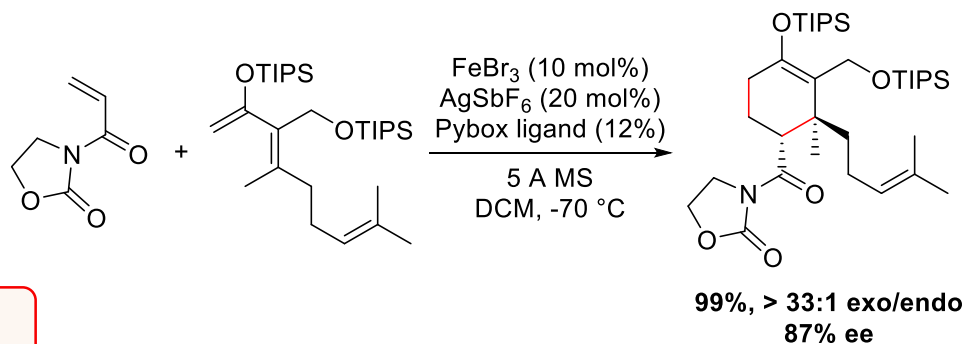
In catalytic hydrogenation:



Introduction

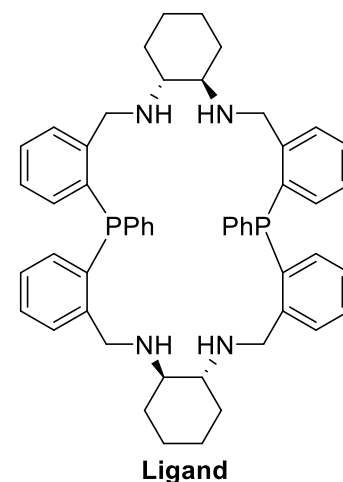
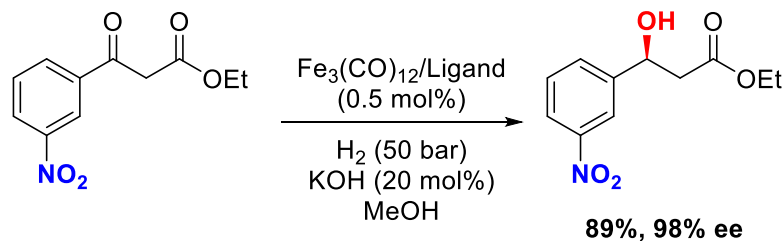
Broad range of applications:

As Lewis acid: Diels-Alder, Friedel-Crafts, ...



As catalyst in oxidation: C-H functionalization

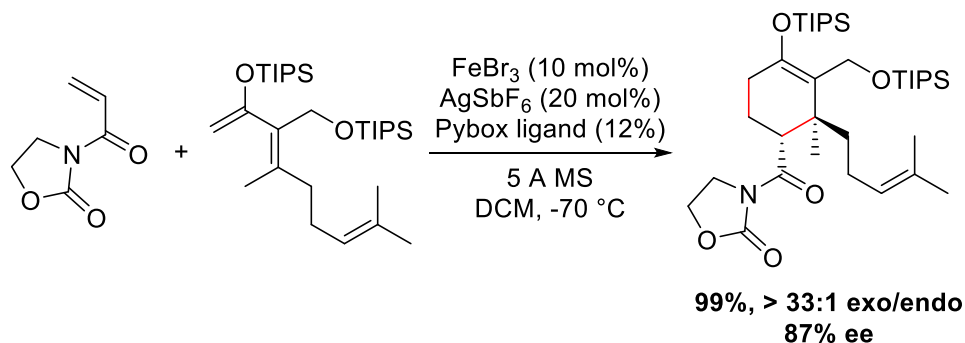
In catalytic hydrogenation:



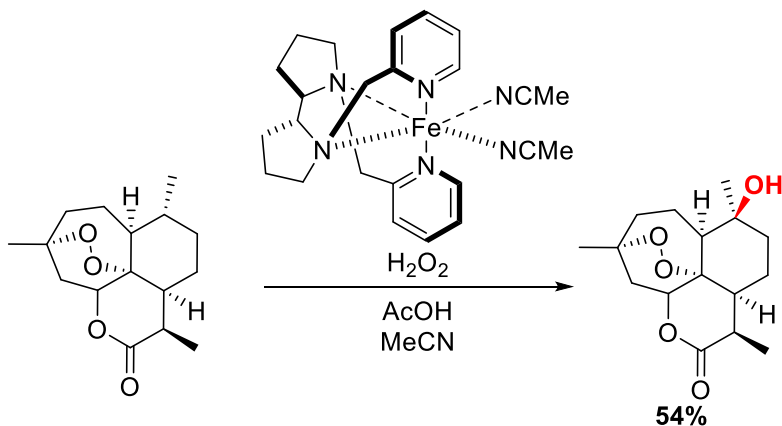
Introduction

Broad range of applications:

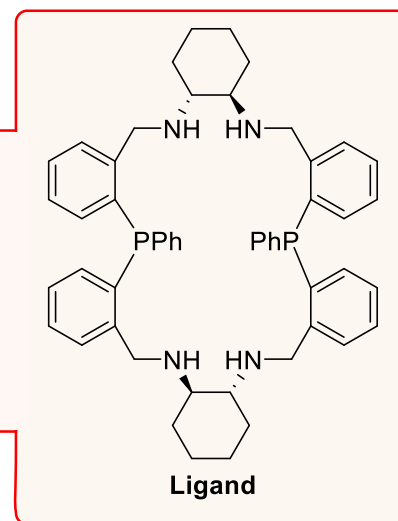
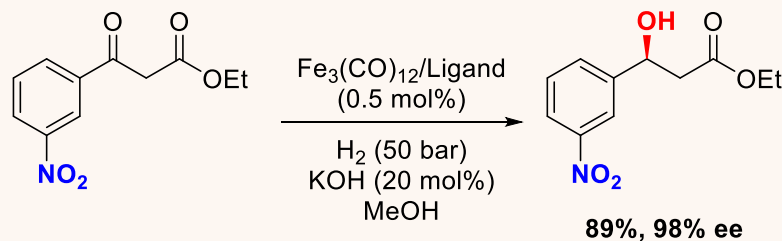
As Lewis acid: Diels-Alder, Friedel-Crafts, ...



As catalyst in oxidation: C-H functionalization



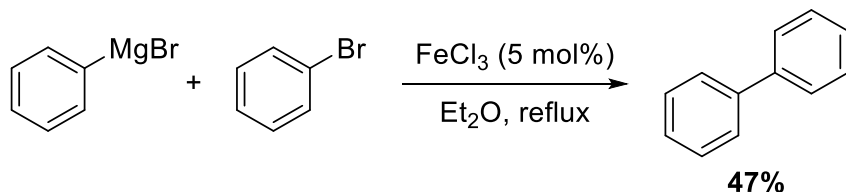
In catalytic hydrogenation:



Preliminary work

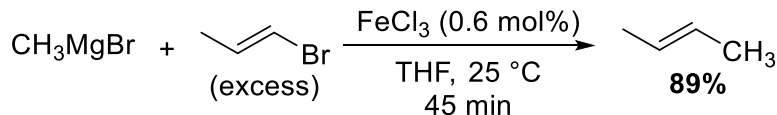
Initial report by Kharash, 1941

- Exploring the effect of metallic halides (Fe, Co, Ni, ...) on the reaction of ArMgBr and RX

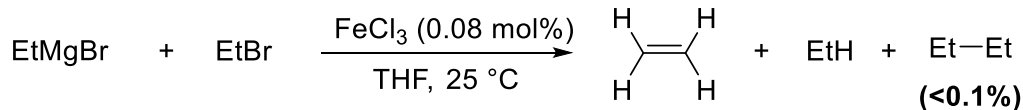


Development of Fe-catalyzed Kumada-Corriu cross coupling (Kochi, 1971)

- Applicable to alkenyl bromide and Grignard reagents



- Alkyl bromides converted in corresponding alkenes

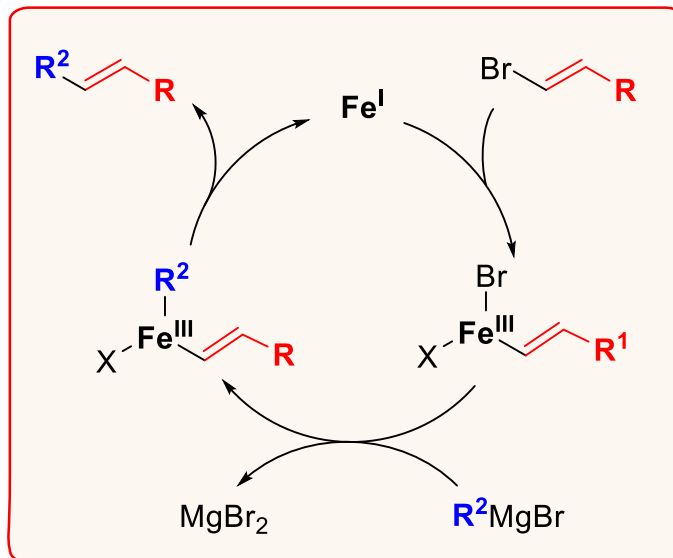


Further developed only 27 years later by Cahiez

Preliminary work

Proposed mechanism:

Fe^I/Fe^{III} catalytic cycle

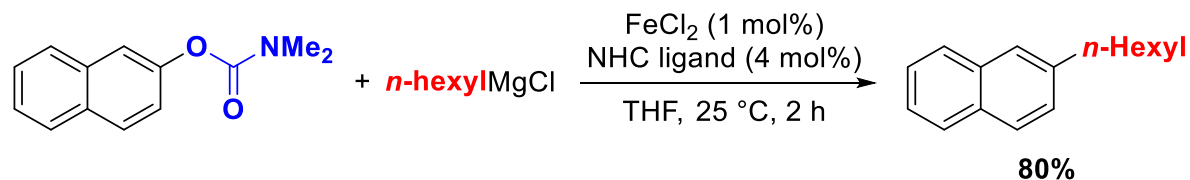


→ Intense ESR spectrum comparable with the one of **HFe^I(dppe)₂**

Recent progress in Kumada-Corriu cross-coupling

Applied to a broad range of electrophiles R-X:

→ X= Cl, Br, I, F, OTs, OTf, OPiv, OCO₂R, OCONMe₂, OPO(OR)₂, SO₂Cl, SO₂R, ...



Z.-J. Shi et al., *J. Am. Chem. Soc.* **2009**, *131*, 14656-14657

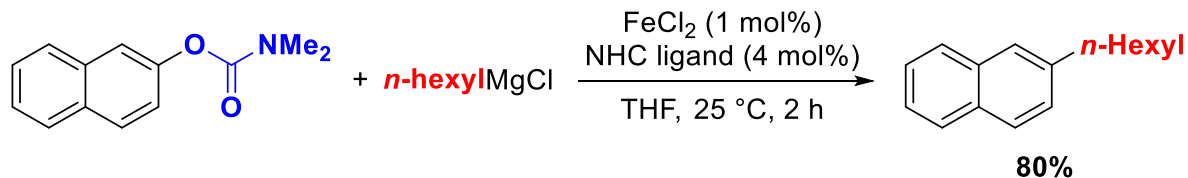
Fürstner et al., *J. Org. Chem.* **2004**, *69*, 3943-3949

Fürstner et al., *Angew. Chem. Int. Ed.* **2016**, *55*, 6051–6056

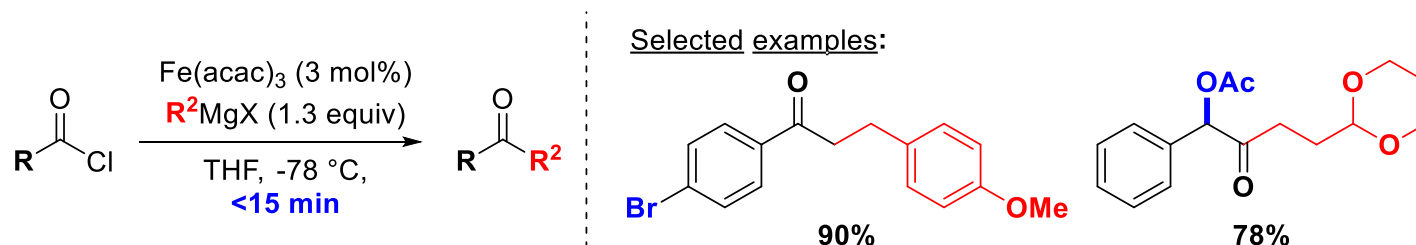
Recent progress in Kumada-Corriu cross-coupling

Applied to a broad range of electrophiles R-X:

→ X= Cl, Br, I, F, OTs, OTf, OPiv, OCO₂R, OCONMe₂, OPO(OR)₂, SO₂Cl, SO₂R, ...



Very reactive but selective:



Z.-J. Shi et al., *J. Am. Chem. Soc.* **2009**, *131*, 14656-14657

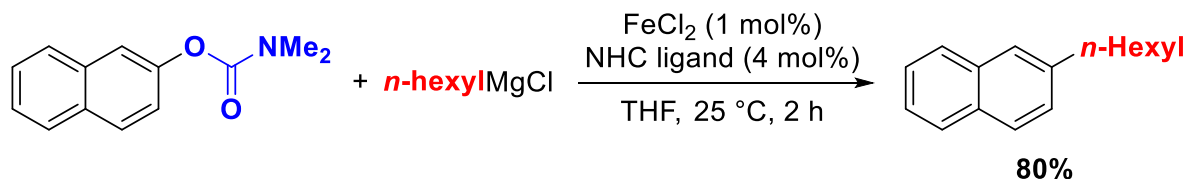
Fürstner et al., *J. Org. Chem.* **2004**, *69*, 3943-3949

Fürstner et al., *Angew. Chem. Int. Ed.* **2016**, *55*, 6051-6056

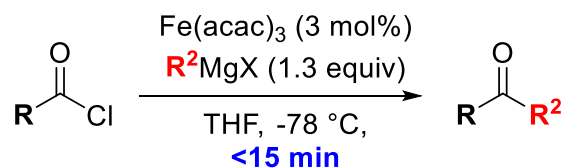
Recent progress in Kumada-Corriu cross-coupling

Applied to a broad range of electrophiles R-X:

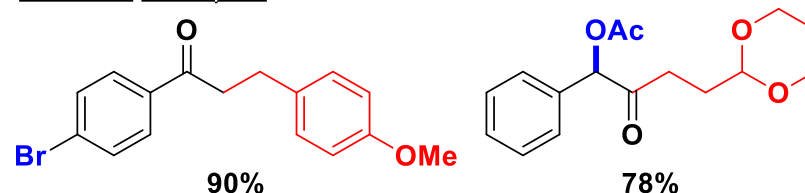
→ X= Cl, Br, I, F, OTs, OTf, OPiv, OCO₂R, OCONMe₂, OPO(OR)₂, SO₂Cl, SO₂R, ...



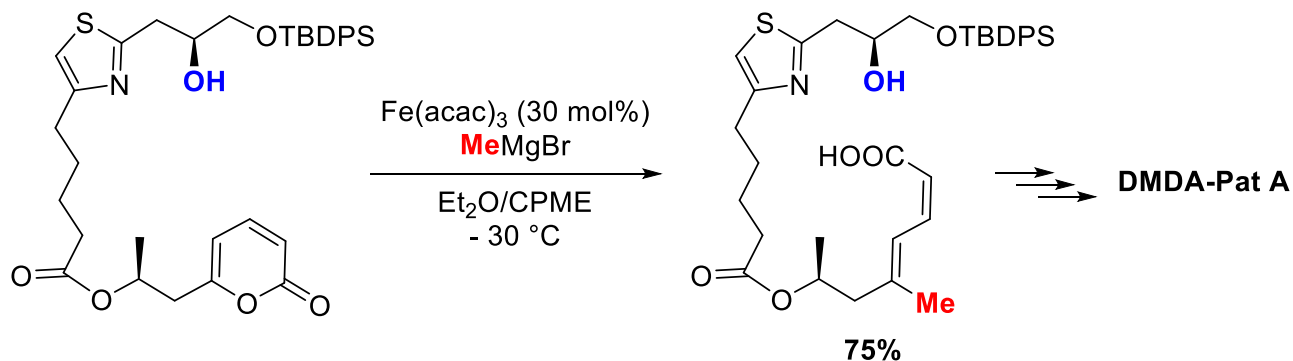
Very reactive but selective:



Selected examples:



New reactivity:



Z.-J. Shi et al., *J. Am. Chem. Soc.* **2009**, *131*, 14656-14657

Fürstner et al., *J. Org. Chem.* **2004**, *69*, 3943-3949

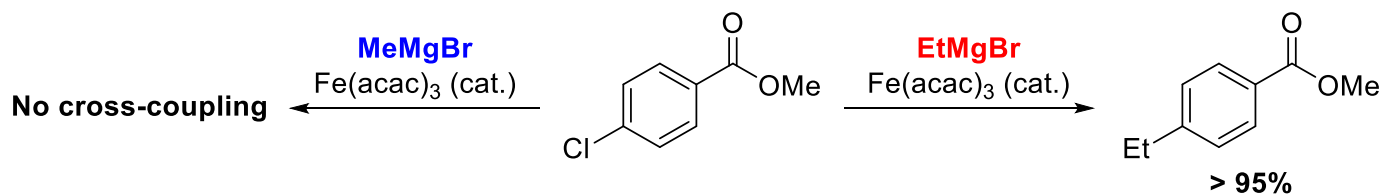
Fürstner et al., *Angew. Chem. Int. Ed.* **2016**, *55*, 6051-6056

Recent progress in Kumada-Corriu cross-coupling

Centered on the mechanism:

→ Several proposed: $\text{Fe}^{-\text{II}}/\text{Fe}^0$, $\text{Fe}^0/\text{Fe}^{\text{II}}$, $\text{Fe}^{\text{I}}/\text{Fe}^{\text{III}}$, $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$, $\text{Fe}^{\text{II}}/\text{Fe}^{\text{IV}}$

→ Highly dependent on the conditions (Nucleophiles, ligands, solvents, additives)



→ Both one- and two-electron process possible

→ Difficult elucidation of the mechanism:

- Paramagnetic nature of many iron species
- Air/thermal sensitivity of most reactive iron intermediates



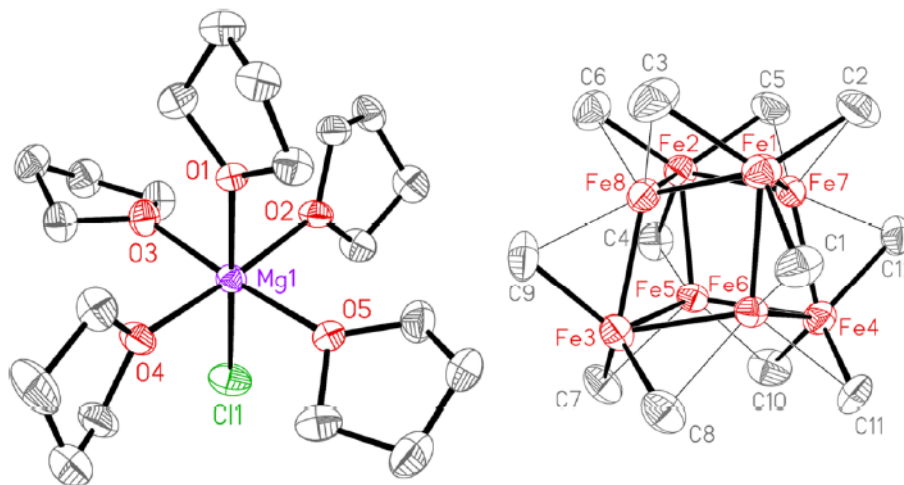
Numerous techniques applied:

- Electron paramagnetic resonance (EPR)
- Magnetic circular dichroism (MCD)
- ⁵⁷Fe Freeze-trapped Mössbauer spectroscopy
- X-ray diffraction, ...

Recent progress in Kumada-Corriu cross-coupling

Organoferrate intermediates with R¹MgBr without β-hydrogen (Me, Ph, ...)

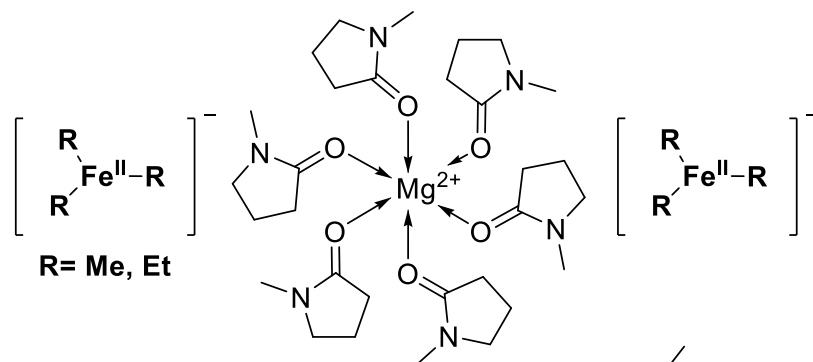
- Fe^I species detected by Kochi → [Fe₈Me₁₂]⁻ [MgCl(THF)₅]⁺ isolated by Neidig *et al.*
- Low activity alone, **require additional MeMgBr**



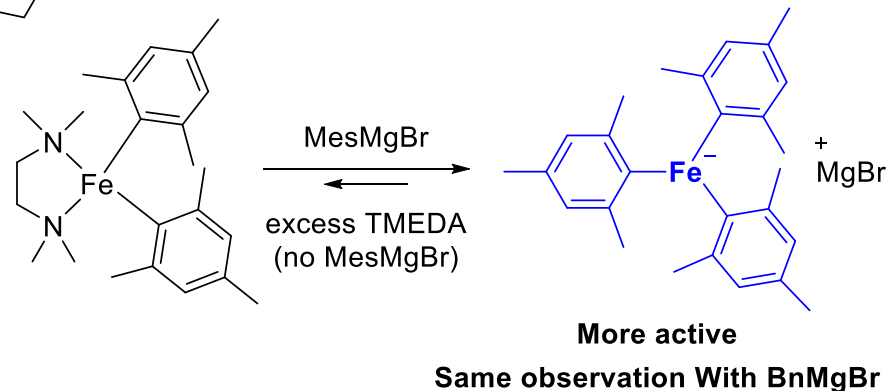
Recent progress in Kumada-Corriu cross-coupling

Organoferrate intermediates with R¹MgBr without β-hydrogen (Me, Ph, ...)

- Switch in presence of NMP or TMEDA:
 - Trialkyl ferrates isolated by Neidig → **catalytically active**



- TMEDA as chaperone



R. B. Bedford et al., *Angew. Chem. Int. Ed.* **2014**, 53, 1804–1808

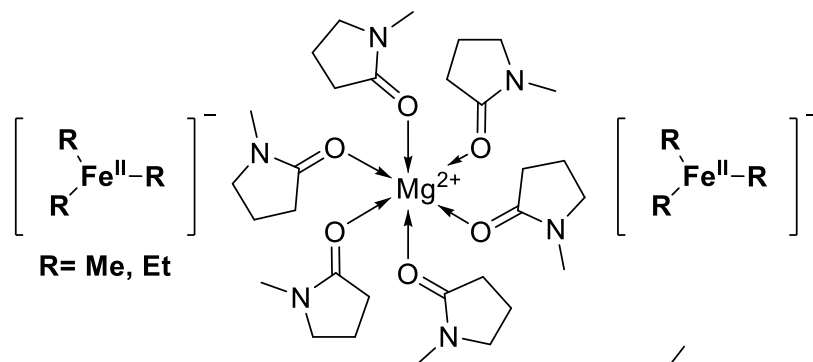
M. L. Neidig et al., *Angew. Chem. Int. Ed.* **2018**, 57, 6496–6500 / *Angew. Chem. Int. Ed.* **2019**, 58, 2769–2773

S. Sandt, A. J. von Wangelin, *Angew. Chem. Int. Ed.* **2020**, 59, 5434–5437

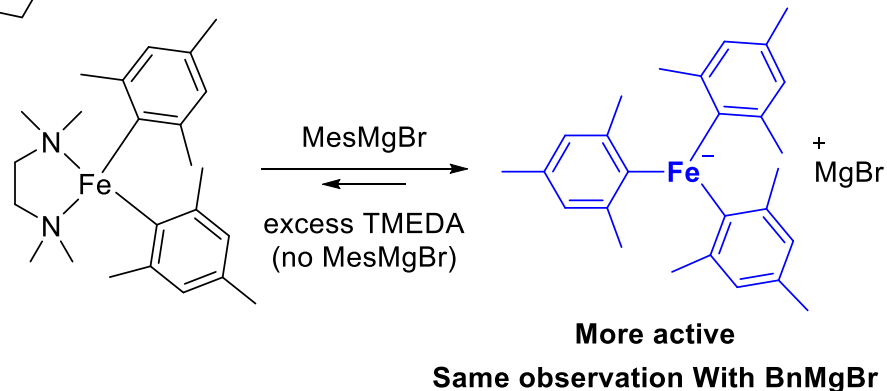
Recent progress in Kumada-Corriu cross-coupling

Organoferrate intermediates with R¹MgBr without β-hydrogen (Me, Ph, ...)

- Switch in presence of NMP or TMEDA:
 - Trialkyl ferrates isolated by Neidig → **catalytically active**



- TMEDA as chaperone



→ **Exact mechanism not fully understood...** (≠ for trialkyl ferrate than iron cluster)

R. B. Bedford et al., *Angew. Chem. Int. Ed.* **2014**, 53, 1804–1808

M. L. Neidig et al., *Angew. Chem. Int. Ed.* **2018**, 57, 6496–6500 / *Angew. Chem. Int. Ed.* **2019**, 58, 2769–2773

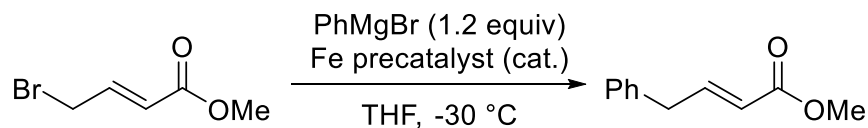
S. Sandt, A. J. von Wangelin, *Angew. Chem. Int. Ed.* **2020**, 59, 5434–5437

Recent progress in Kumada-Corriu cross-coupling

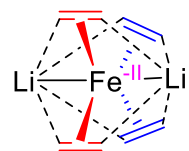
Fe^{-II}/Fe⁰ mechanism proposed with R¹MgX (R¹ with β-H)

→ Fe^{-II}(MgX)₂ speculated (first by Bogdanovic)

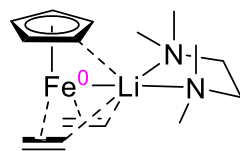
→ Several pre-catalysts synthesized and tried



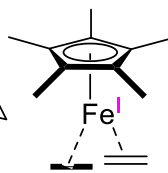
Fe pre-catalyst:



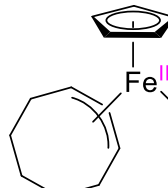
<10 min, 94%



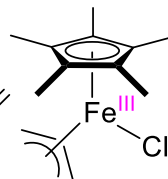
30 min, 45%



30 min, 50%



30 min, 46%



30 min, 73%



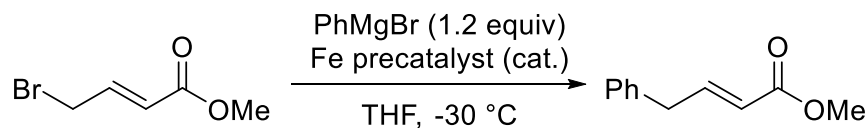
Higher activity for Fe^{-II} pre-catalyst

Recent progress in Kumada-Corriu cross-coupling

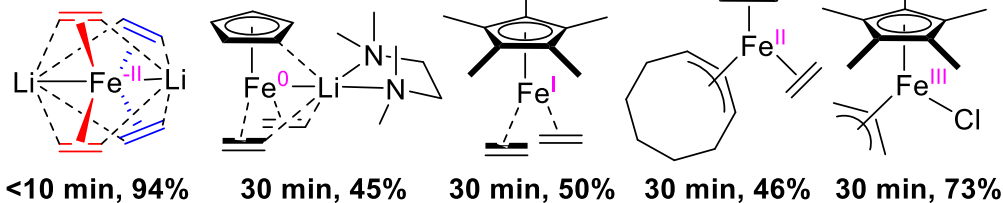
Fe^{II}/Fe⁰ mechanism proposed with R¹MgX (R¹ with β-H)

→ Fe^{II}(MgX)₂ speculated (first by Bogdanovic)

→ Several pre-catalysts synthesized and tried

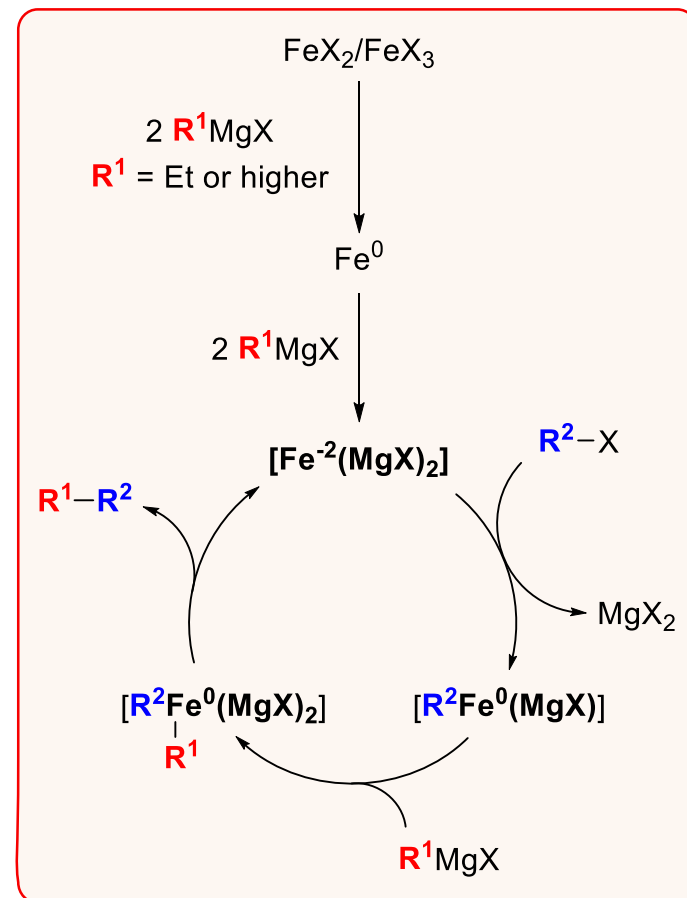


Fe pre-catalyst:



➡ Higher activity for Fe^{II} pre-catalyst

→ Proposed mechanism:

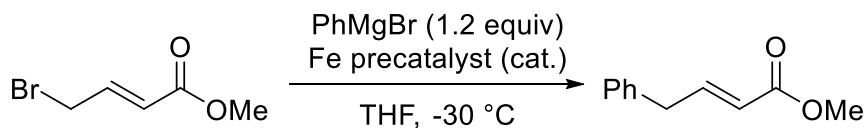


Recent progress in Kumada-Corriu cross-coupling

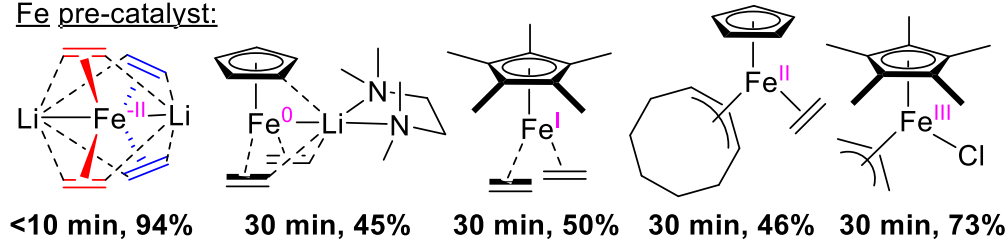
Fe^{-II}/Fe⁰ mechanism proposed with R¹MgX (R¹ with β-H)

→ Fe^{-II}(MgX)₂ speculated (first by Bogdanovic)

→ Several pre-catalysts synthesized and tried



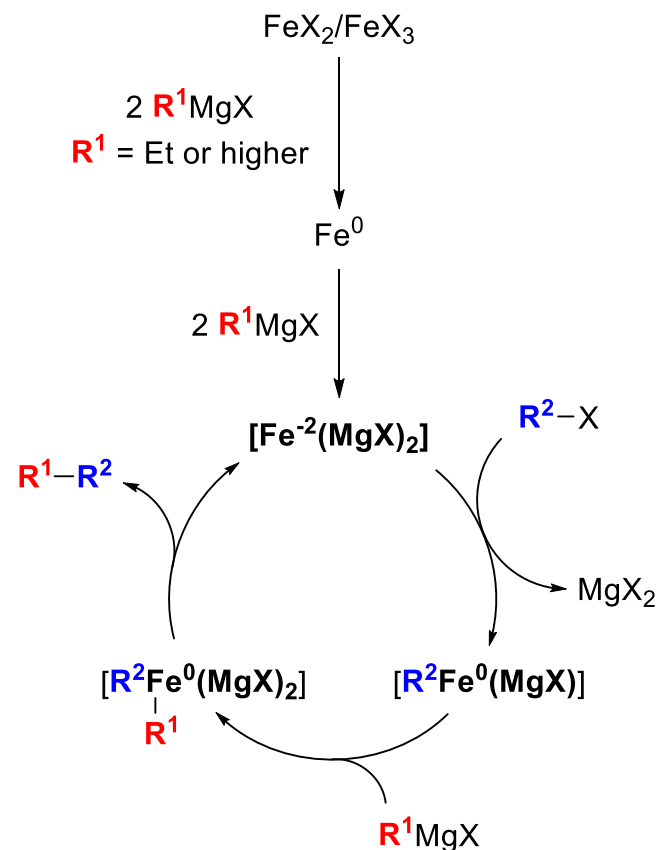
Fe pre-catalyst:



➔ Higher activity for Fe^{-II} pre-catalyst

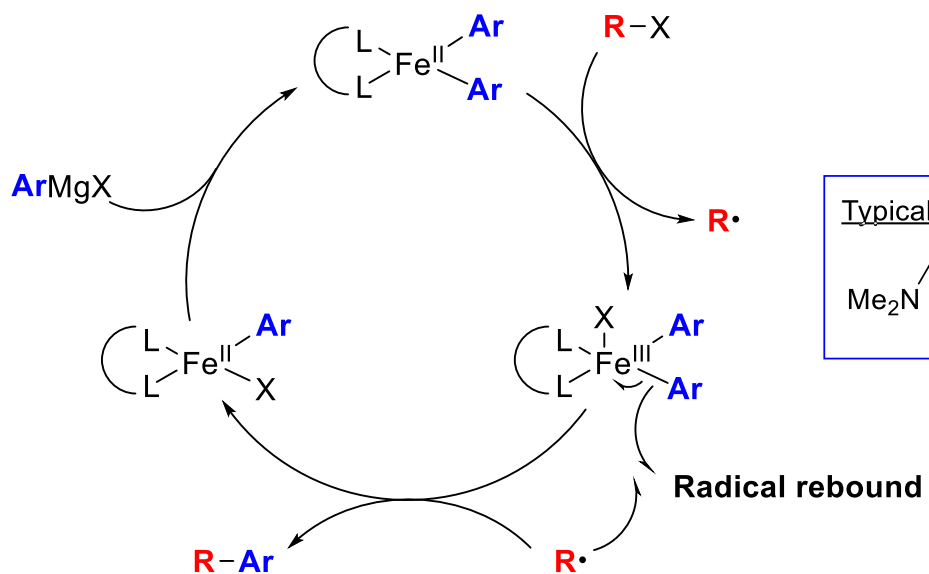
→ Proposed mechanism:

- However:
- Possible concomitant mechanisms
 - Only pre-catalysts
 - Different ligands → strong influence

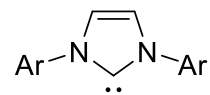
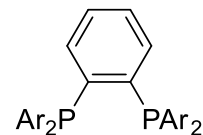
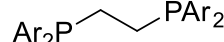
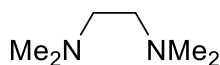


Recent progress in Kumada-Corriu cross-coupling

$\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ catalytic cycle proposed in many cases

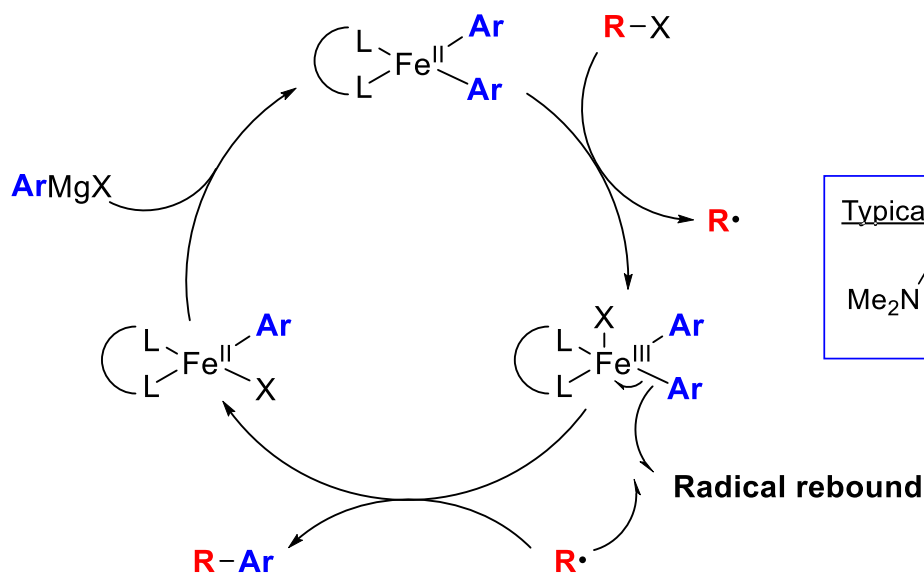


Typically used ligands:

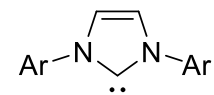
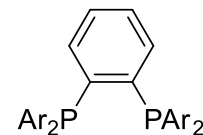
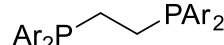
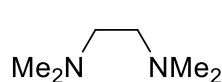


Recent progress in Kumada-Corriu cross-coupling

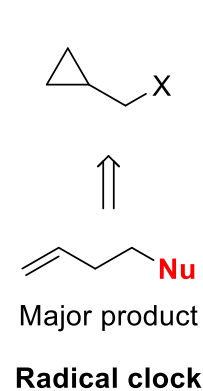
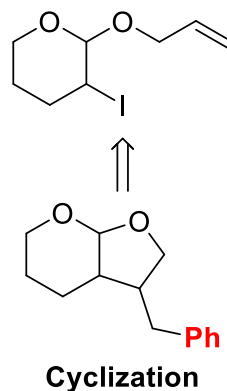
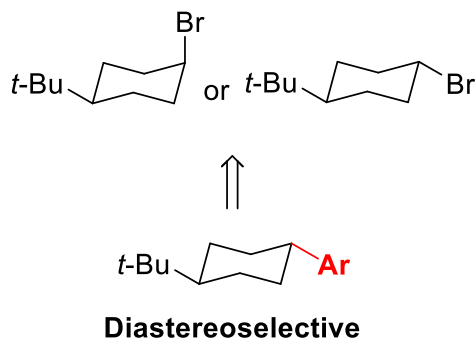
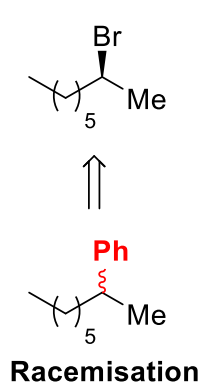
$\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ catalytic cycle proposed in many cases



Typically used ligands:



→ Whatever the mechanism, several experiments in favor of alkyl radicals:

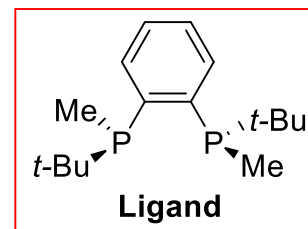
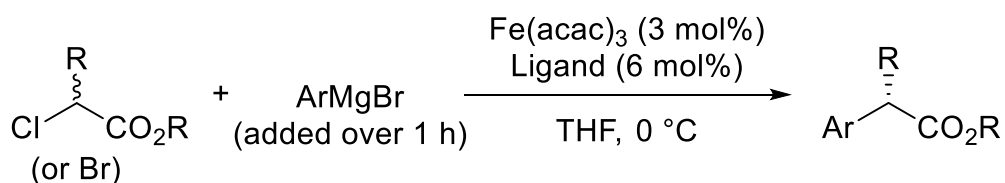


C.-J. Wallentin *et al.*, *ACS Catal.* **2016**, *6*, 1640–1648
 M. Nakamura *et al.*, *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687.
 A. Fürstner *et al.*, *Angew. Chem. Int. Ed.* **2004**, *43*, 3955–3957

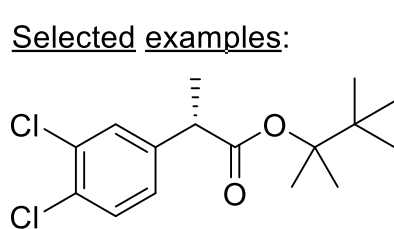
Enantioselective Kumada-Corriu cross-coupling

Only one report to date (Nakamura *et al.* 2015)

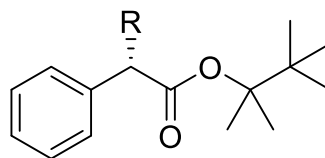
- Enantioconvergent coupling of aryl Grignard reagents with α -chloroesters



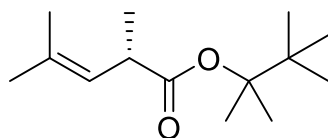
Selected examples:



88% (90:10 er)

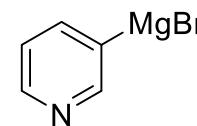


R = Et, 67% (88:12 er)
R = *i*-Bu, 38% (74:26 er)
R = CH₂OMe, 42% (77:23 er)

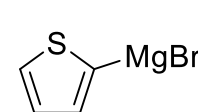


52% (91:9 er)

With:



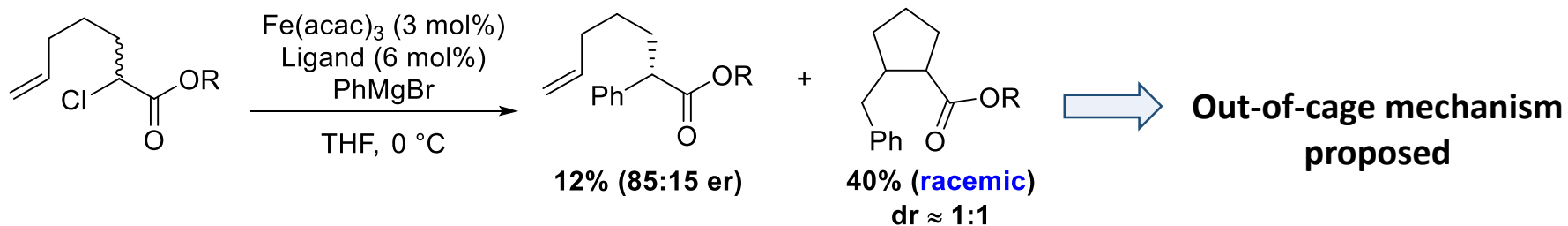
0%



0%

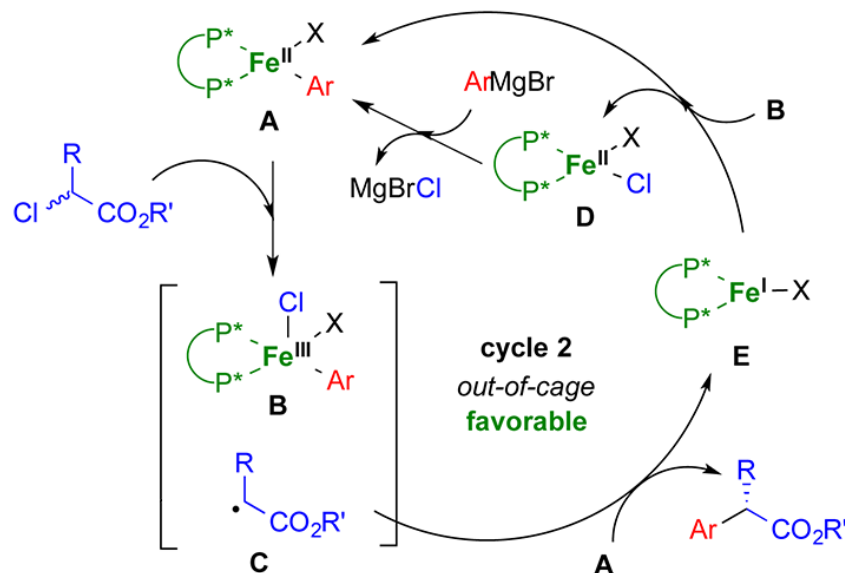
Enantioselective Kumada-Corriu cross-coupling

Mechanistic investigations:



→ First-order relationship between [Fe cat.] and ratio not cyclized-cyclized

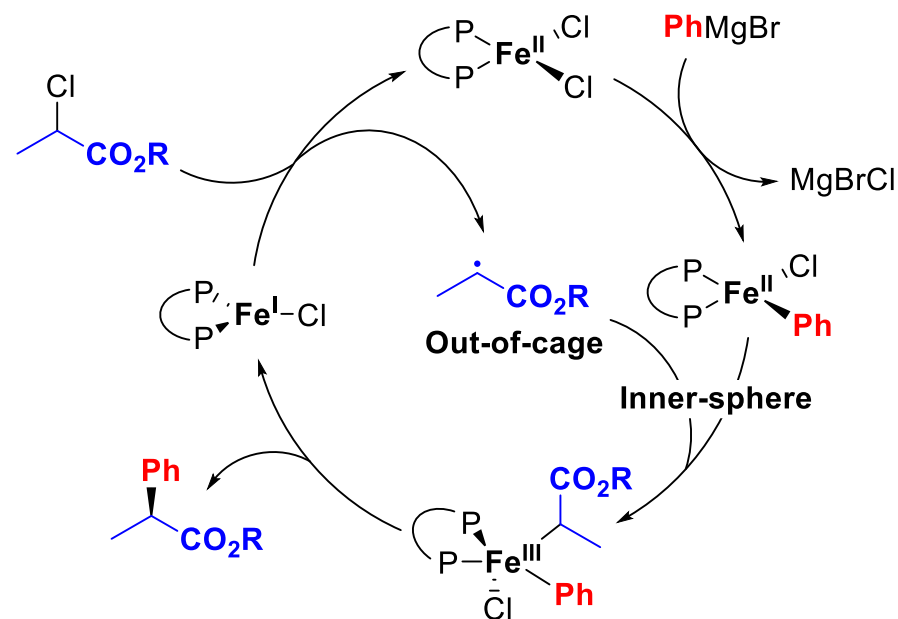
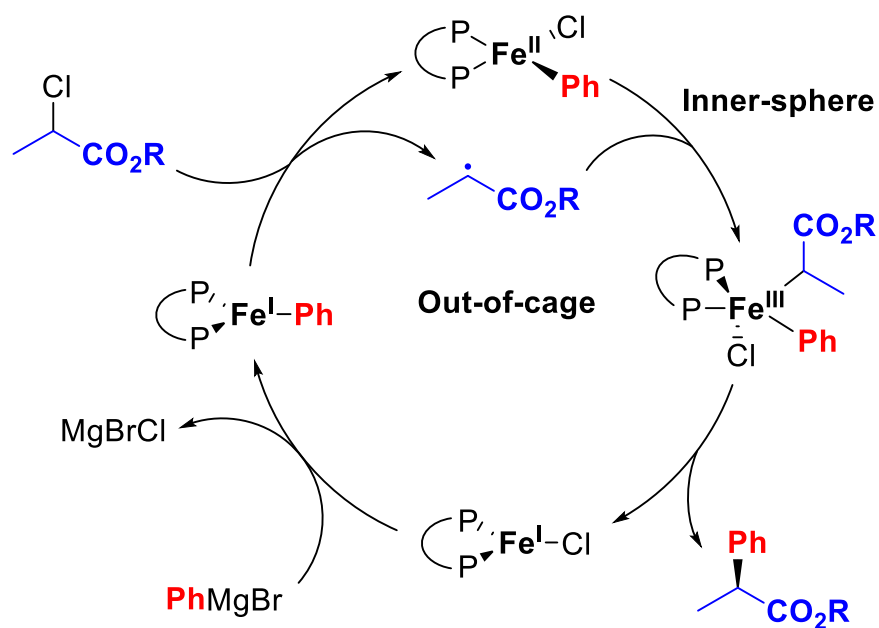
Bimetallic mechanism proposed:



Enantioselective Kumada-Corriu cross-coupling

Computational studies:

→ 2 slightly different mechanisms proposed



→ C-Cl activation high in energy for Fe^{II} species → Fe^I more favorable

→ Dropwise addition of Grignard reagent important to avoid Fe^{II}PhPh (biphenyl formation)

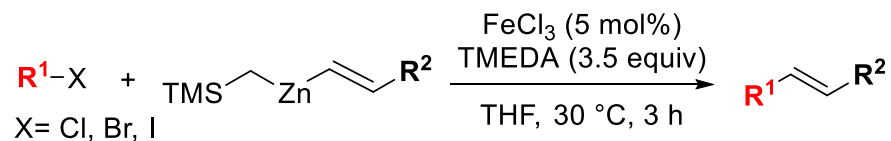
→ Inner-sphere out-of-cage mechanism

O. Gutierrez *et al.*, *J. Am. Chem. Soc.* **2017**, *139*, 16126–16133

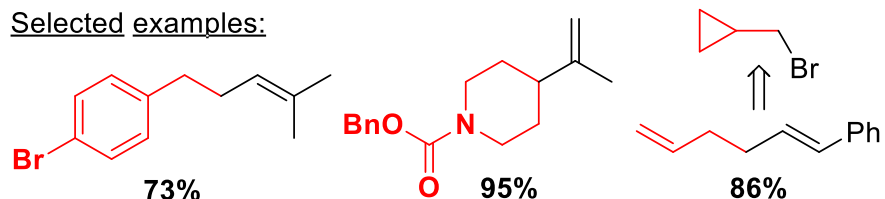
M. Nakamura, K. Morokuma *et al.*, *J. Am. Chem. Soc.* **2017**, *139*, 16117–16125

New development in Negishi cross-coupling

First reported with vinyl zinc reagents

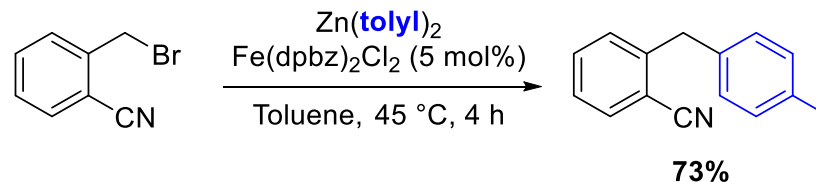


Selected examples:

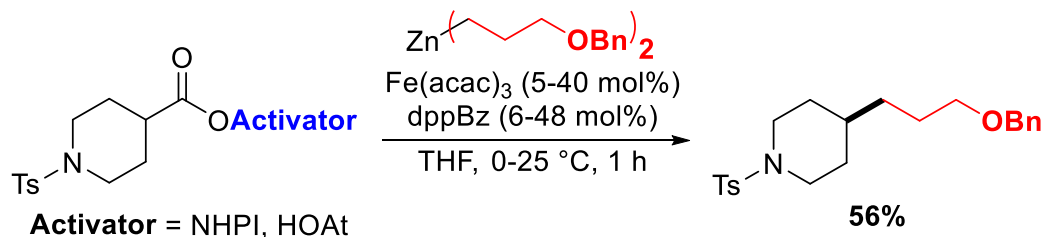


Only scarce numbers of reports

- With benzyl-X:



- Extended further with redox-active esters (1°, 2°, 3° alkyl-COOH/ Ar- and R₂Zn):



M. Nakamura *et al.*, *Org. Lett.* **2009**, *11*, 4496-4499

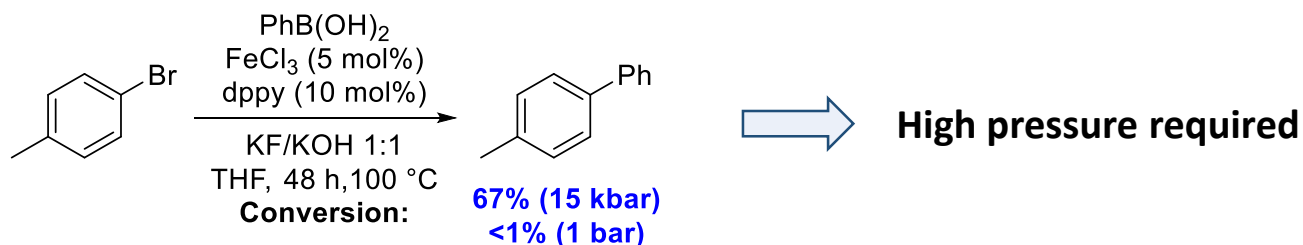
R. B. Bedford *et al.*, *Chem. Commun.* **2009**, 600-602 / *Angew. Chem. Int. Ed.* **2013**, *52*, 1285-1288

P. S. Baran *et al.*, *J. Am. Chem. Soc.* **2016**, *138*, 11132-11135

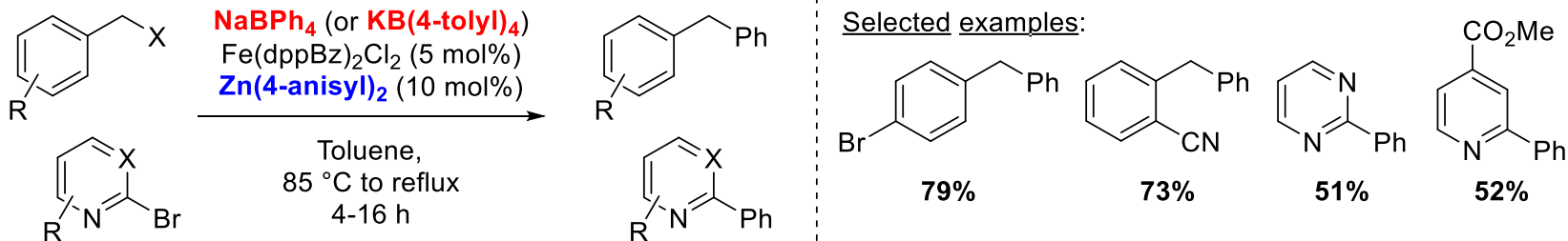
Progress in Suzuki-Miyaura cross-coupling

Few reports → Difficulty with the transmetalation/reduction step

First report of Fe-catalyzed Suzuki-Miyaura cross-coupling (Hor *et al.*, 2008)

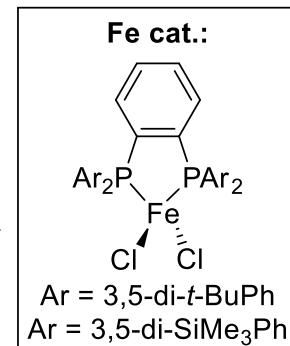
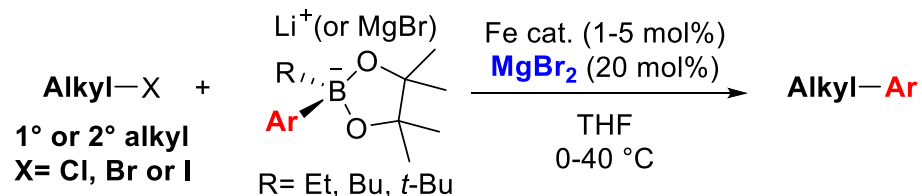


Solution: Use activated borate as nucleophile (Bedford *et al.*, 2009)

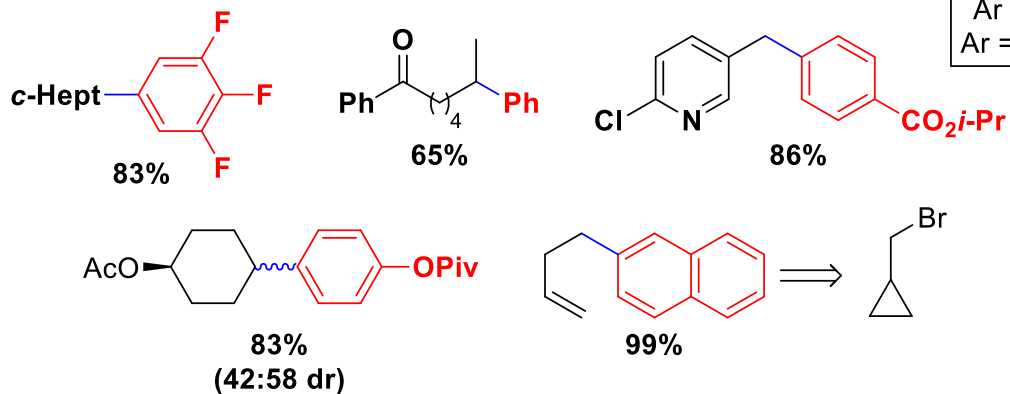


Progress in Suzuki-Miyaura cross-coupling

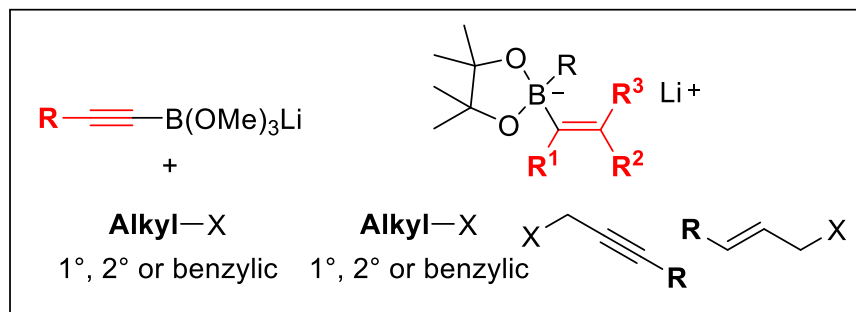
Nakamura 2010



Selected examples:



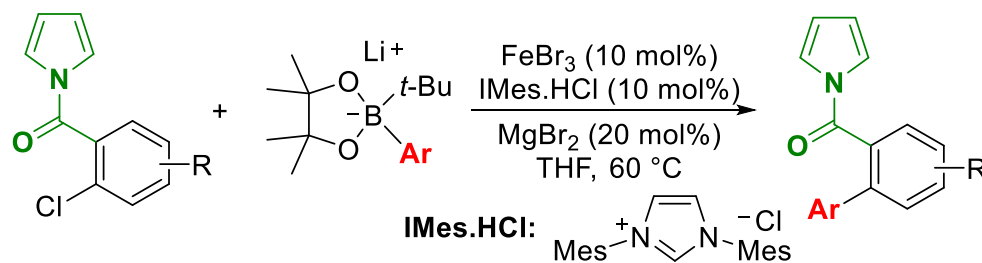
Extension of the scope



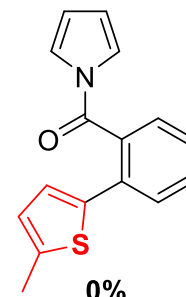
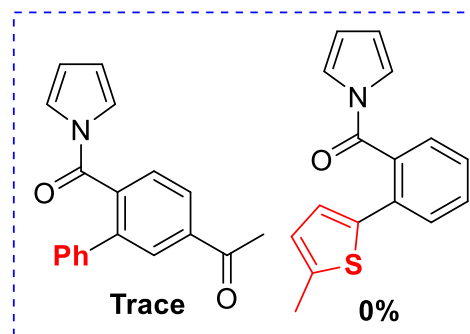
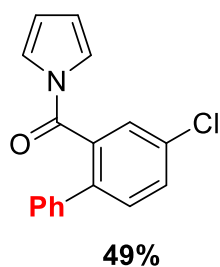
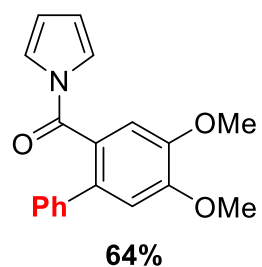
Progress in Suzuki-Miyaura cross-coupling

Only few reports with aryl electrophile

- First reports → Due to palladium contaminations (articles retracted later)
- Observed as side-product with 2-halobenzyl halides (< 41%)
- Directing group required (Bedford et al., 2018)



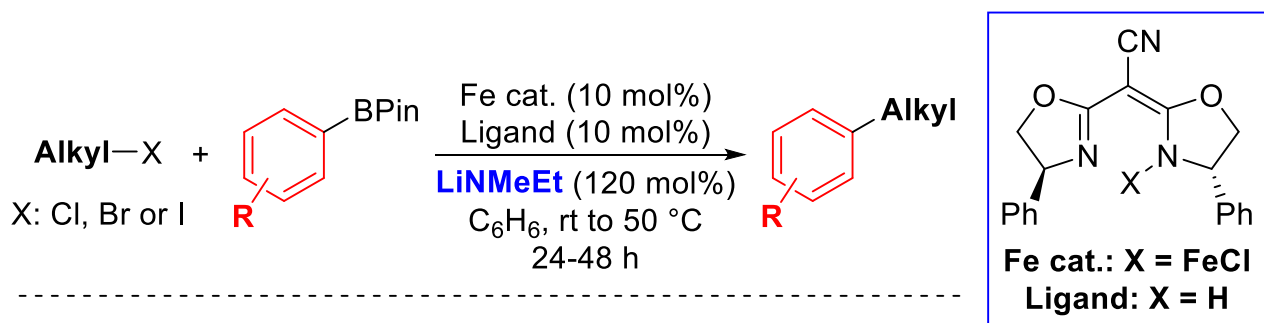
Selected examples:



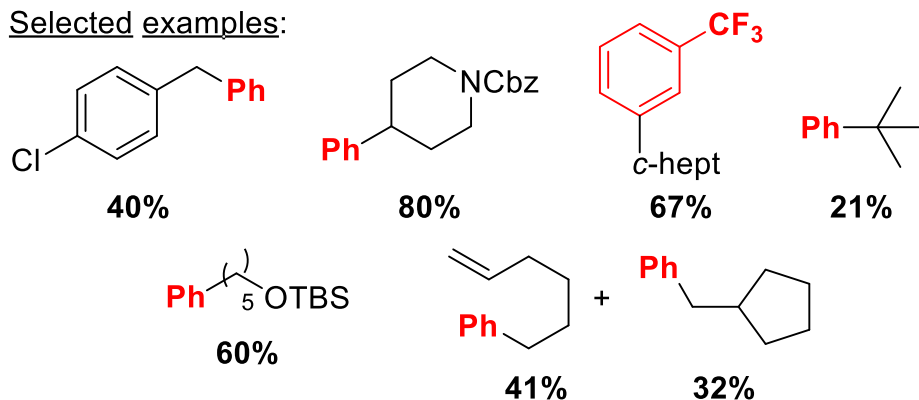
Progress in Suzuki-Miyaura cross-coupling

Byers's work with ligand tuning

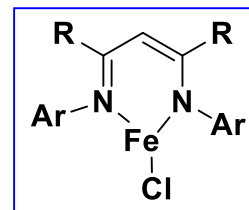
- Alkoxide to help the transmetallation → Iron aggregates: inactive
- Anionic ligand and amide base → improved transmetallation / monomeric iron species



Selected examples:



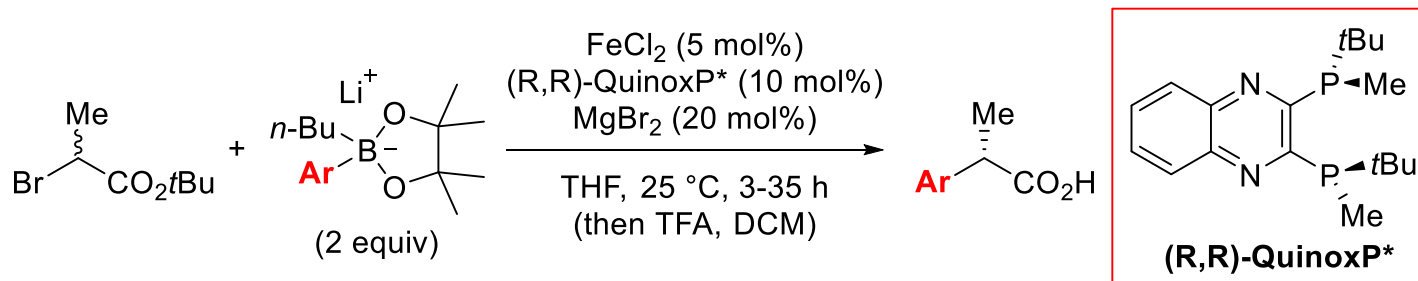
- Improvement of the scope (heteroaromatic-BPin, 3° alkyl) and efficiency with:



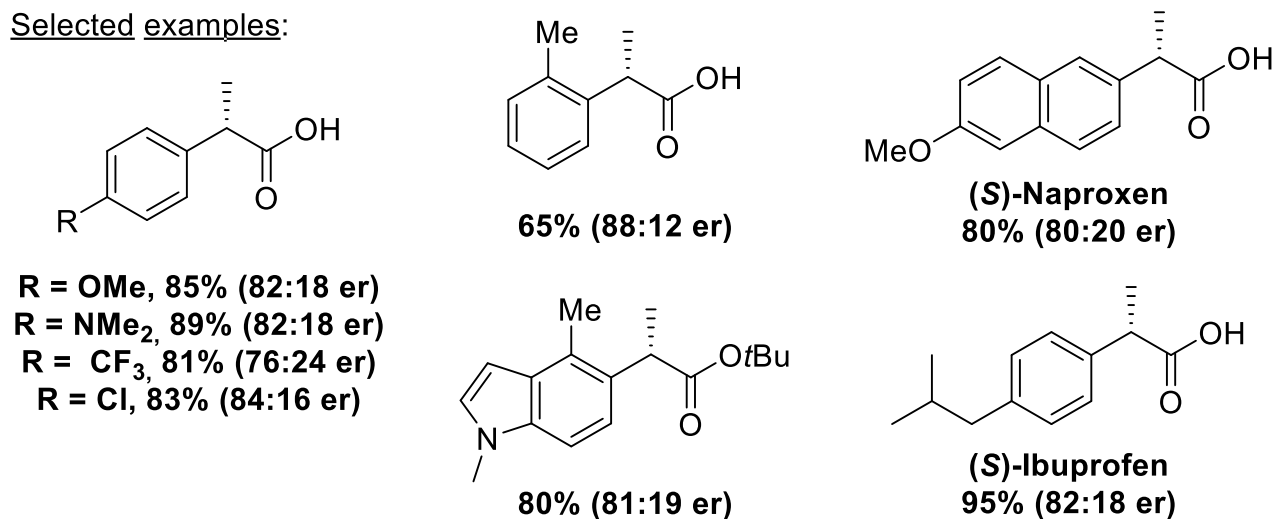
Enantioselective cross-coupling

First report of enantioselective Fe-catalyzed Suzuki-Miyaura cross-coupling (Nakamura *et al.* 2019)

- Enantioconvergent coupling of lithium arylborates with α -bromoesters



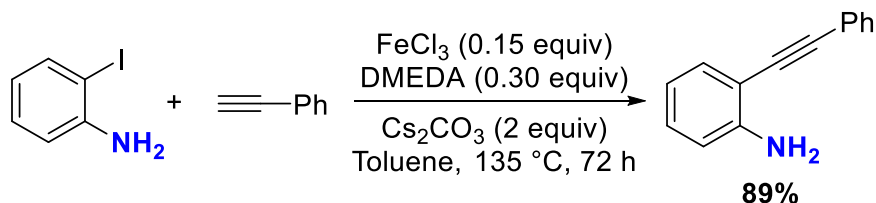
Selected examples:



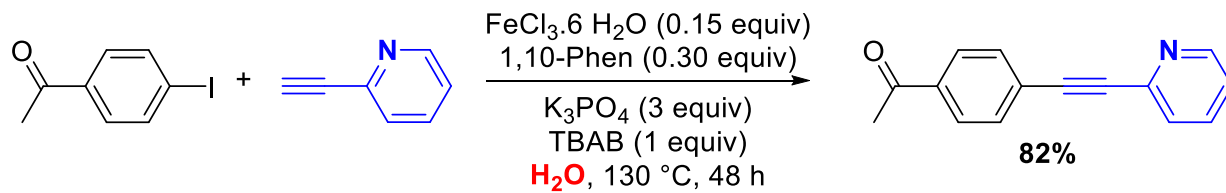
Point on Fe-catalyzed Sonogashira

Still under developed ...

- First report by Bolm and coworkers



- Designed in water

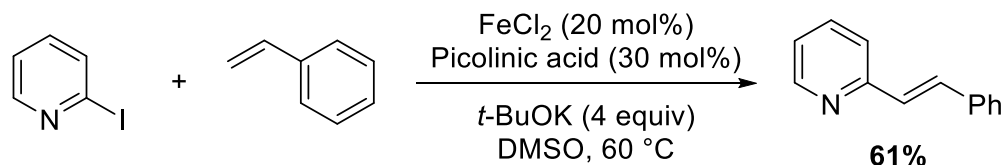


→ Few other reports but only very high temperature

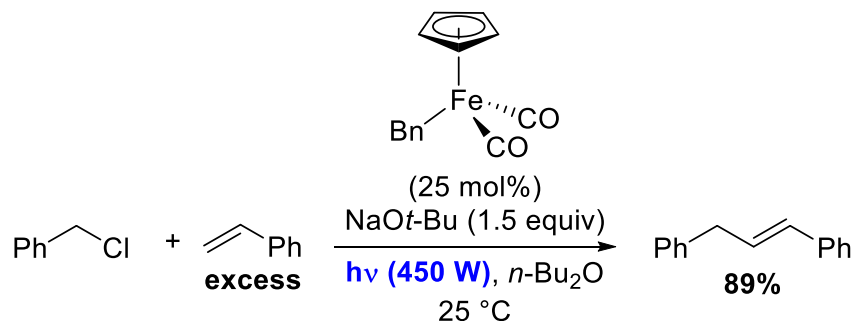
Fe catalysis in Heck-type cross-coupling

Only few reports

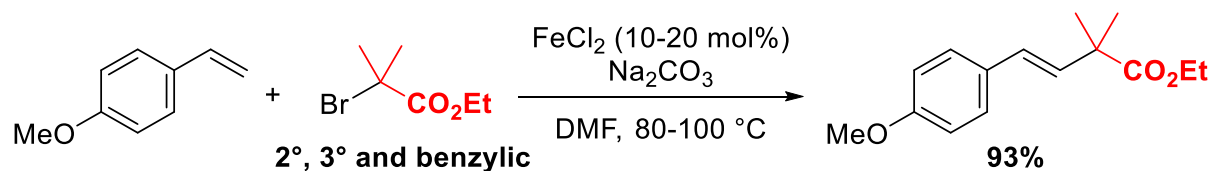
- Initial report by Vogel



- Extended to benzylic substrates via UV-irradiated iron catalyst



- Applied in 2017 to alkyl electrophiles



P. Vogel *et al.*, *Adv. Synth. Catal.* **2008**, 350, 2859–2864
G. W. Waldhart, N. P. Mankad, *J. Organomet. Chem.* **2015**, 793, 171-174
S. P. Thomas *et al.*, *ACS Catal.* **2017**, 7, 2353–2356

Conclusion and Outlooks

- Iron-catalyzed Kumada-Corriu cross-coupling **well developed**
 - Very **fast** reaction, even at low temperature
 - Highly **chemoselective**
 - Cheap catalyst, often **without ligand**
 - Less-sensitive to β -hydride elimination



However, **mechanisms still not fully understood ...**

- Almost **no enantioselective version**
- Use of less-nucleophilic partner **still underdeveloped**

Conclusion and Outlooks

- Iron-catalyzed Kumada-Corriu cross-coupling **well developed**
 - Very **fast** reaction, even at low temperature
 - Highly **chemoselective**
 - Cheap catalyst, often **without ligand**
 - Less-sensitive to β -hydride elimination



However, **mechanisms still not fully understood ...**

- Almost **no enantioselective version**
- Use of less-nucleophilic partner **still underdeveloped**



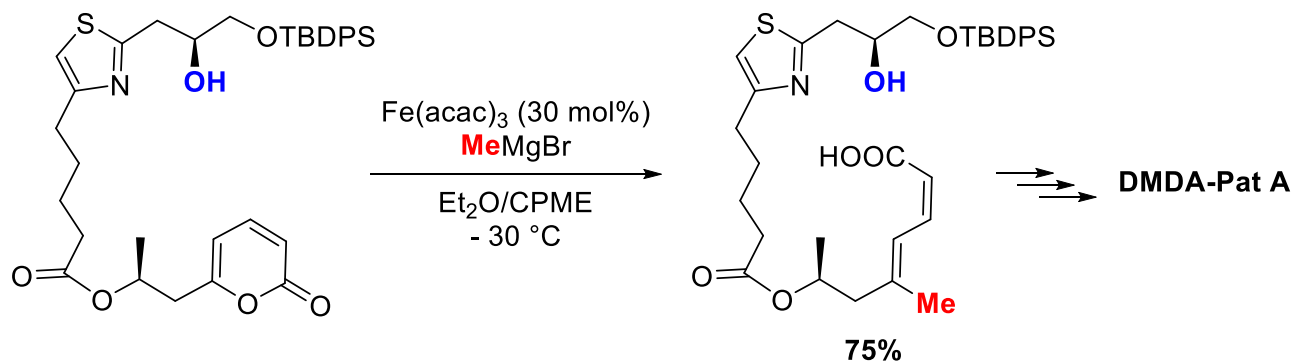
Tuning of the ligands might be key ...

Thank you for your attention

Questions

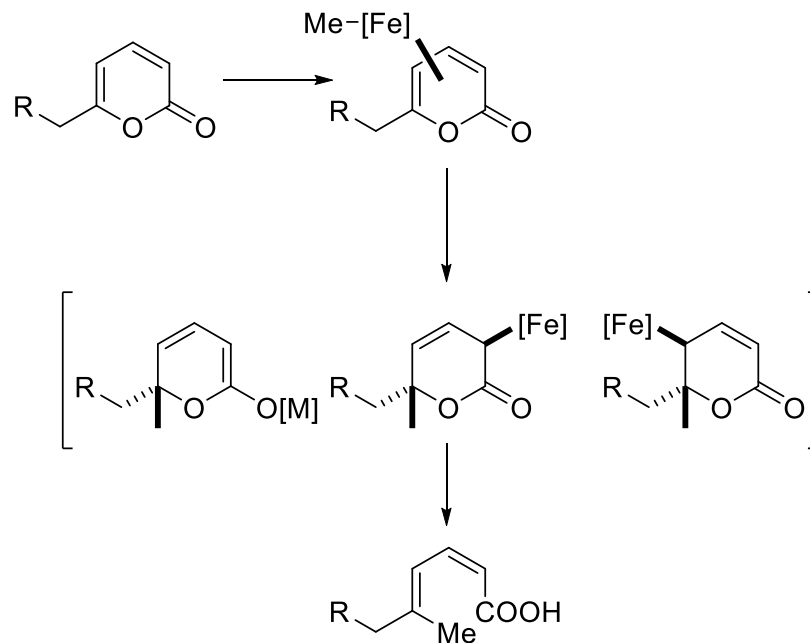
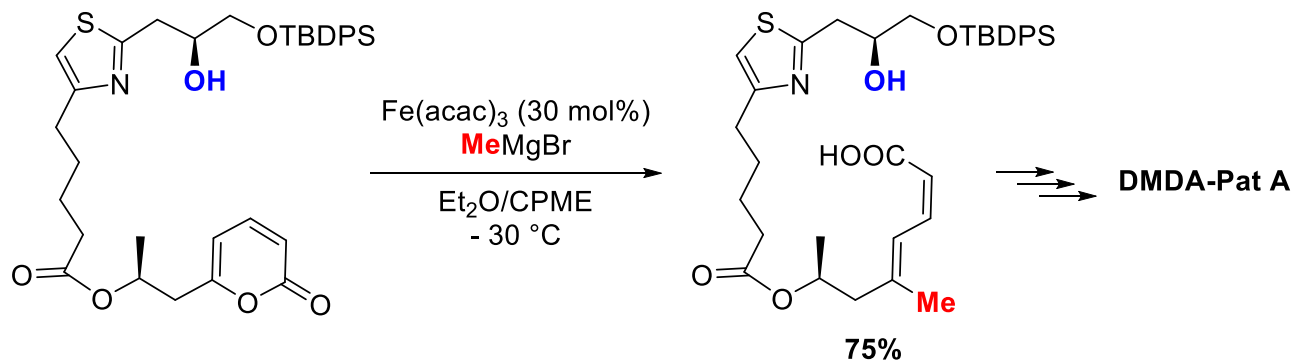
Questions 1

Can you suggest a mechanism for this transformation ?



Questions 1

Can you suggest a mechanism for this transformation ?



Questions 2

Propose a mechanism for the reduction of Fe^{II} to $\text{Fe}^{-\text{II}}$ and Fe^{III} to $\text{Fe}^{-\text{II}}$

Questions 2

Propose a mechanism for the reduction of Fe^{II} to $\text{Fe}^{-\text{II}}$ and Fe^{III} to $\text{Fe}^{-\text{II}}$

