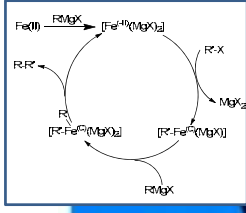## Advances in Well defined Iron Catalysts for Cross Coupling
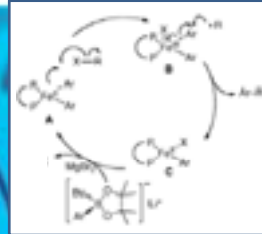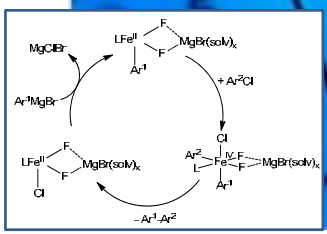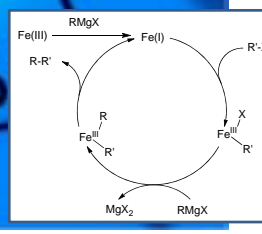

Michael J. Ingleson

Overview

• **Strengths and Complexities of Fe in Catalysis**

• **Brief Historical Perspective - From Kochi onwards**

• **Advances in C-X / C-M Fe catalysed Cross Coupling (over the last 4-5 years)**

• **The Nascent area of direct C-H Arylation using Fe (last 1-2 years)**

• **Conclusions**

Disclaimer: Its Impossible to be comprehensive in this area! A personal selection.

Research Driver

1 Cost + Toxicity

2 Supply chain risks

Iron: Has Key Economic Advantages – but more than that:

Ability to access fundamentally different reactivity to Pd/Ni/Cu with cheap ligands

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Source: Critical raw materials for the EU (July 2010)

Why Well Defined Iron Catalysis?

Classical Common Non Zero Oxidation States

In contrast: Palladium, 0, II, IV
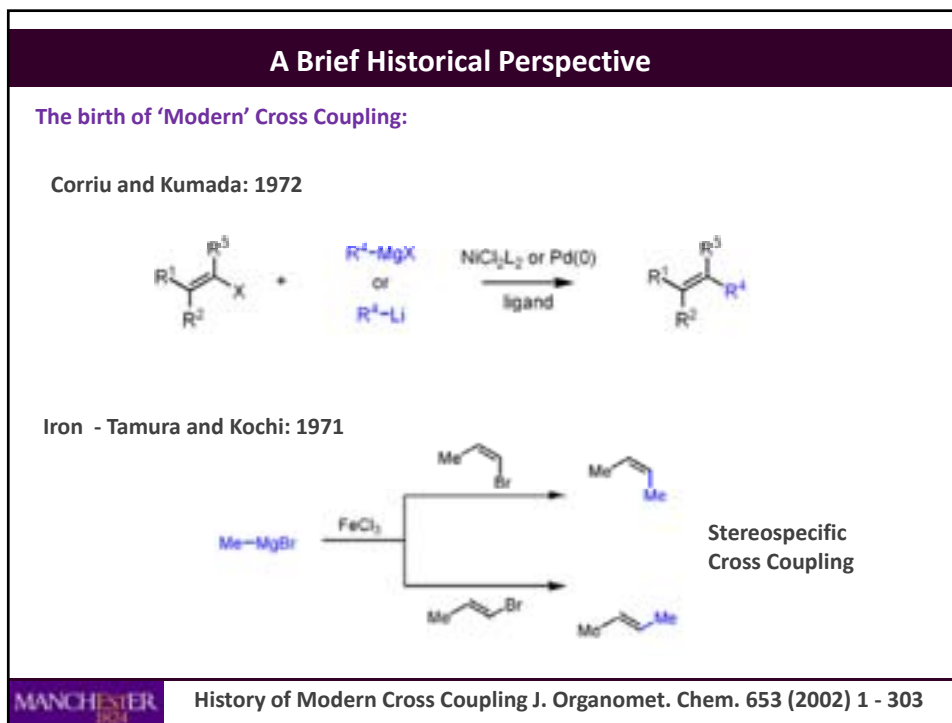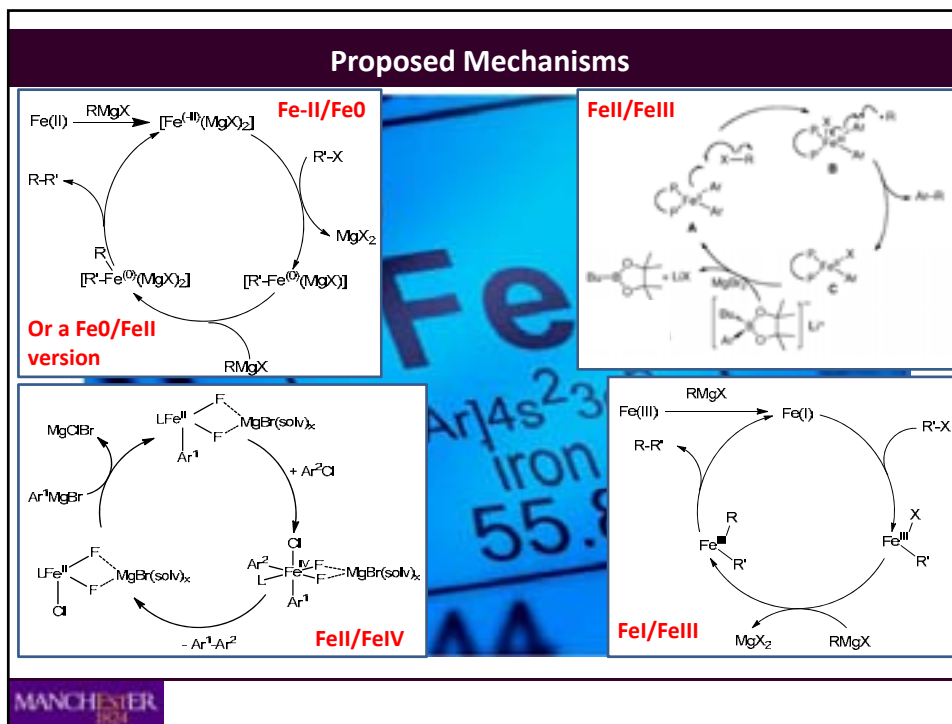

However in reality for Fe :

-II, 0, I, II, III and IV

All these are oxidation states can be important, is dependent on the catalyst / nucleophile / ligand

Predicting reactivity requires understanding of the dominant mechanism

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Proposed Mechanisms

Fe-II/Fe0

Or a Fe0/FeII version

FeII/FeIII

FeII/FeIV

FeI/FeIII

A Brief Historical Perspective

The birth of 'Modern' Cross Coupling:

Corriu and Kumada: 1972

Iron - Tamura and Kochi: 1971

Stereospecific Cross Coupling

History of Modern Cross Coupling J. Organomet. Chem. 653 (2002) 1 - 303

Substrate Scope – Alkenyl Derivatives

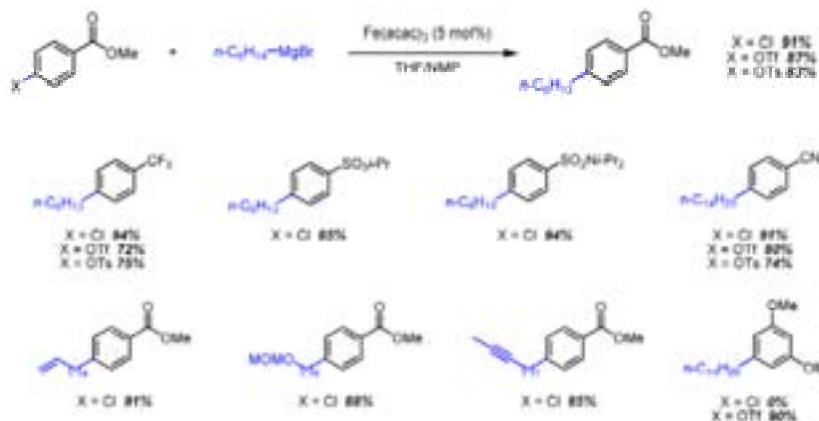**2nd- generation (Broader Substrate scope)**

Key Stabilising ligand
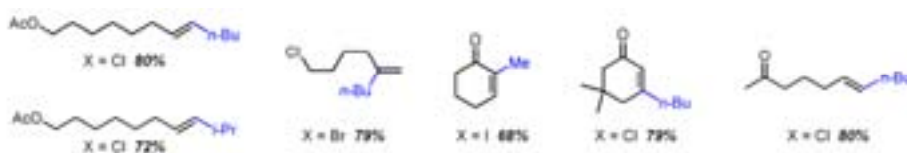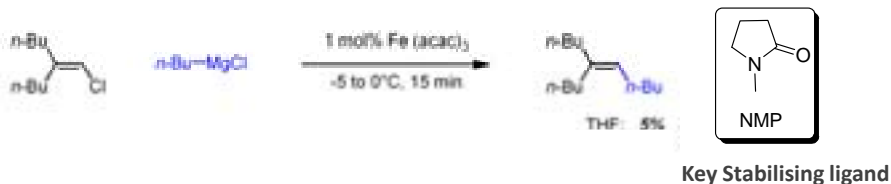
Cahiez, G. et. al. *Synthesis* 1998, 1199.

Substrate Scope – Aryl Derivatives

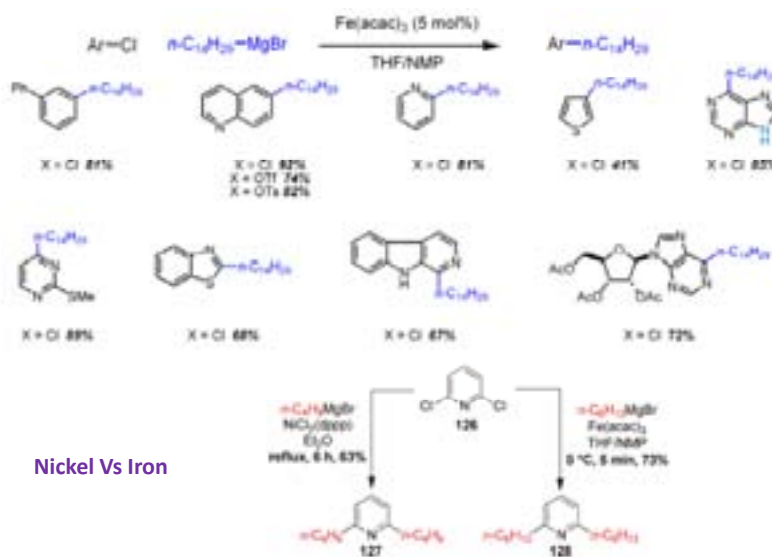**Aryl chlorides, triflates and tosylates superior to aryl bromides/iodides (reduction of C-X) instead**

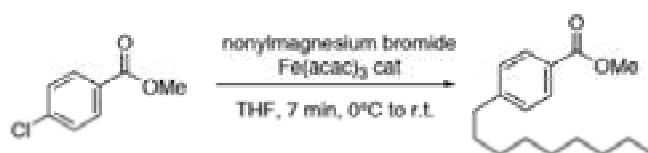**However, Aryl Triflates are generally necessary with electron-rich aryl substrates**

Fürstner, A. et. al. *Angew. Chem. Int. Ed. Engl.* 2002, *41*, 609 and JACS, 2002, 124 13856

Coupling with Heteroaryl Halides

Nickel Vs Iron

Fürstner, A. et. al. *Angew. Chem. Int. Ed. Engl.* 2002, *41*, 609 and JACS, 2002, 124 13856
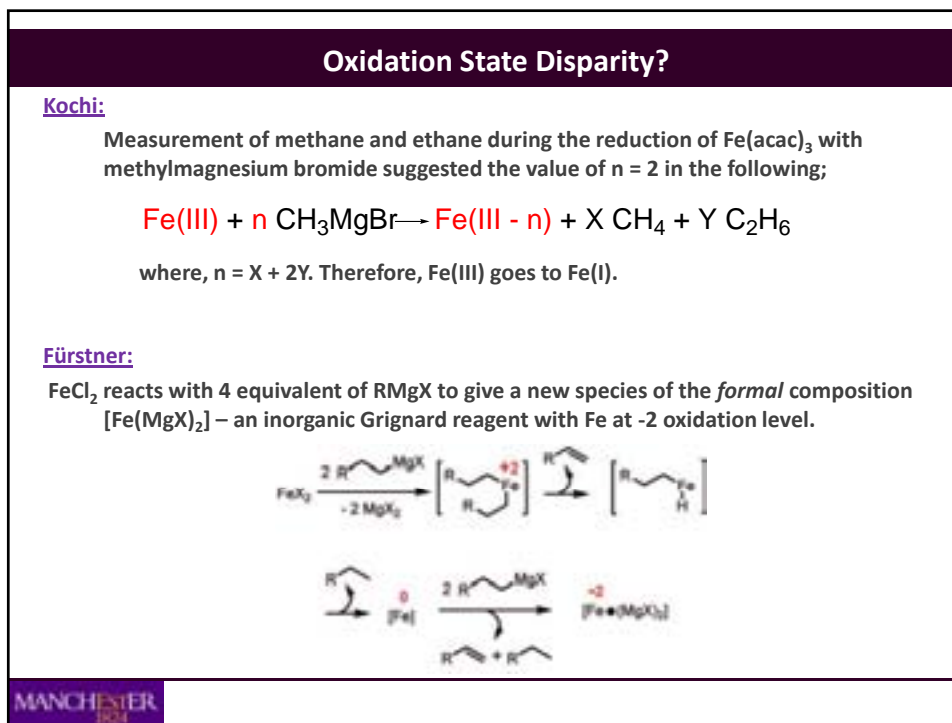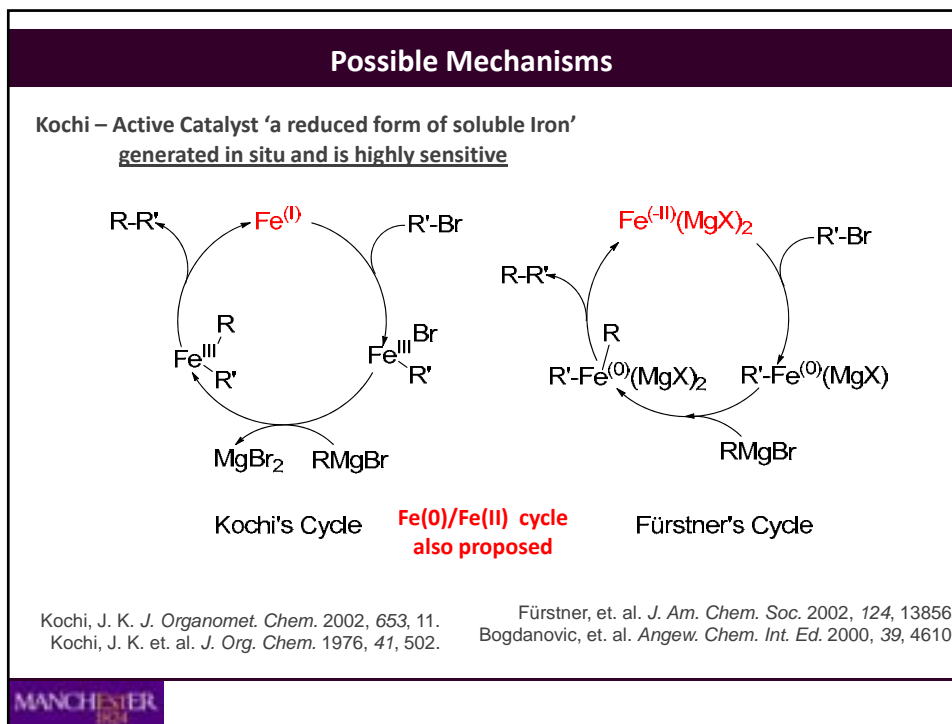
Readily Amenable to scale up

> 17g, 84 % Isolated Yield

Component of Liquid Crystals

Fürstner et al. Org Synth 2005, 81, 33-41

12/7/2011

Possible Mechanisms

Kochi – Active Catalyst 'a reduced form of soluble Iron'
generated in situ and is highly sensitive

Kochi's Cycle   **Fe(0)/Fe(II) cycle also proposed**   Fürstner's Cycle

Kochi, J. K. *J. Organomet. Chem.* 2002, *653*, 11.
Kochi, J. K. et. al. *J. Org. Chem.* 1976, *41*, 502.

Fürstner, et. al. *J. Am. Chem. Soc.* 2002, *124*, 13856.
Bogdanovic, et. al. *Angew. Chem. Int. Ed.* 2000, *39*, 4610.

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Oxidation State Disparity?

Kochi:

Measurement of methane and ethane during the reduction of $Fe(acac)_3$ with methylmagnesium bromide suggested the value of n = 2 in the following;

$$Fe(III) + n\ CH_3MgBr \longrightarrow Fe(III - n) + X\ CH_4 + Y\ C_2H_6$$

where, n = X + 2Y. Therefore, Fe(III) goes to Fe(I).

Fürstner:

$FeCl_2$ reacts with 4 equivalent of RMgX to give a new species of the *formal* composition $[Fe(MgX)_2]$ – an inorganic Grignard reagent with Fe at -2 oxidation level.
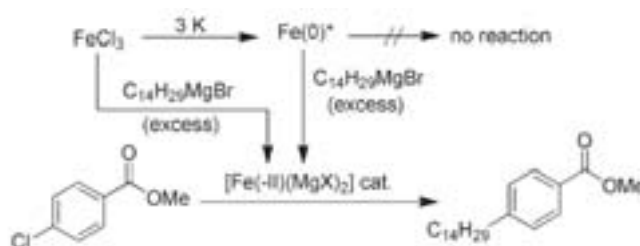

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6

At least Two Different Reactivity Manifolds

i. The presence of β-hydrides is essential

ii. Fe(0) is inactive

Fürstner *et al.,* J. AM. CHEM. SOC. 2008, *130, 8773–8787*
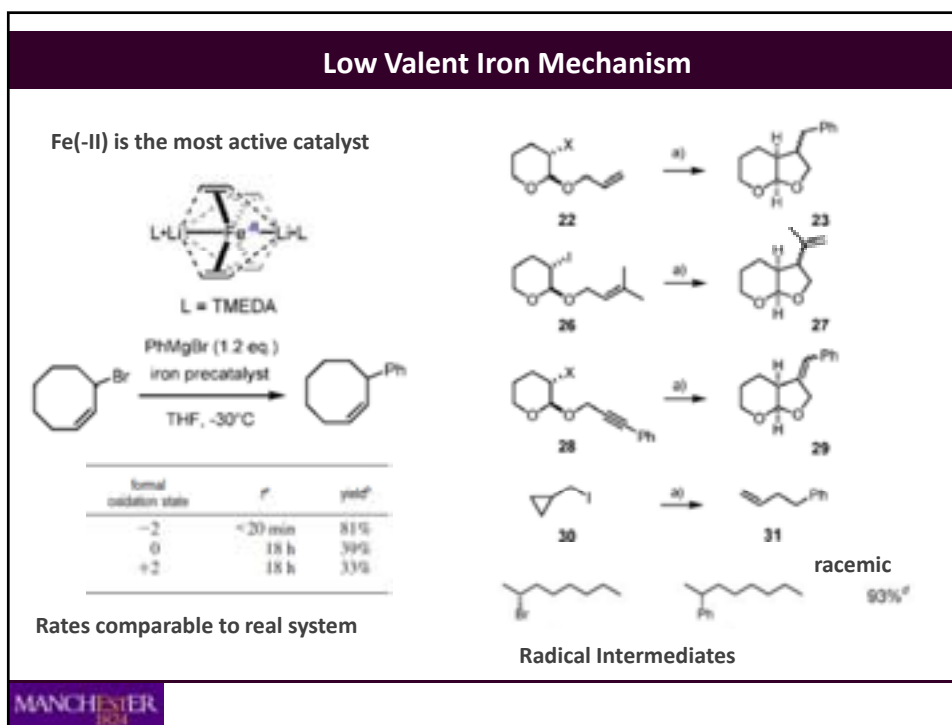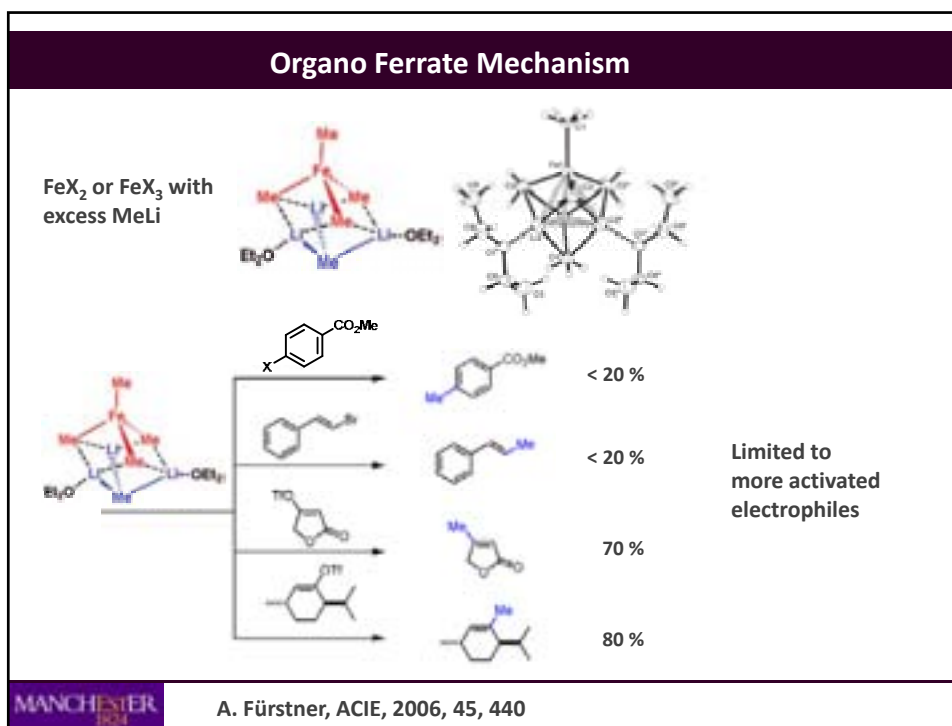
Divergent Catalytic Cycles
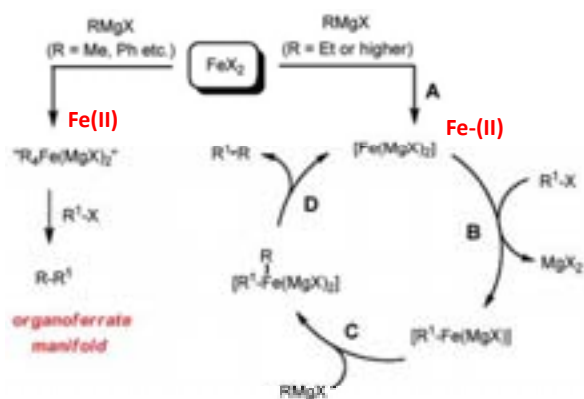
Fe(II)

Fe-(II)

Aryl, vinyl, allyl and Methyl Grignard Reagents

Without β Hydrides

Grignard Reagents with β Hydrides

Fürstner *et al.,* J. AM. CHEM. SOC. 2008, *130, 8773–8787*

12/7/2011

Organo Ferrate Mechanism

FeX$_2$ or FeX$_3$ with excess MeLi

< 20 %

< 20 %

70 %

80 %

Limited to more activated electrophiles

A. Fürstner, ACIE, 2006, 45, 440

Low Valent Iron Mechanism

Fe(-II) is the most active catalyst

L = TMEDA

PhMgBr (1.2 eq.)
iron precatalyst

THF, -30°C

formal oxidation state	t	yield
−2	<20 min	81%
0	18 h	39%
+2	18 h	33%

Rates comparable to real system

22 → 23

26 → 27

28 → 29

30 → 31

racemic
93%

Radical Intermediates

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Application to Grignards with no β-hydride

Using the preformed Fe(-II) catalyst (5 mol%, THF -20°C, L = TMEDA)
Enables activation of sp^3 C-X and coupling with ArMgBr

L = TMEDA

Substrate	Product	Yield
		95% (X = OMe)
		67% (X = Cl)
		93% (X = Ph)
		86% (X = NMe₂)
		77%
		94%
		93%
		58%
		74%

Substrate	Product	Yield
		84%
		91%
		87%
		83%
		90%
		86%
		68%

Fürstner *et al.*, J. AM. CHEM. SOC. 2008, *130*, 8773–8787

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Inexpensive/Simpler Catalyst Development

L = TMEDA

1) Whilst achieving sp^3 C-X /ArylMgBr coupling - need simpler, easier to handle catalysts

2) Furthermore these systems have limited applicability in ArylCl + ArylMgBr coupling

Again Need to Overcome:
(i) β-Hydride elimination - alkene formation, and redcution processes
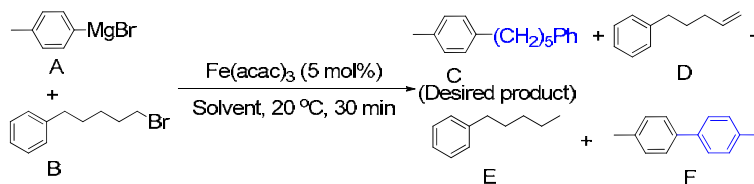(ii) Homocoupling (Kharasch 1940s)

Major by-products in initial Fe catalysed cross-coupling of 1° and 2° alkyl substrates with Aryl Grignard reagents
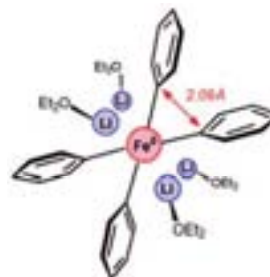
Achieving these goals led to the development of 2 new distinct Catalytic Approaches

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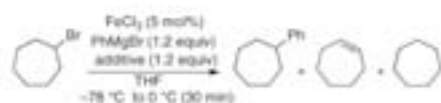## Beyond N-Me-pyrrolidone

Solvent	Product Yield (%)			
	C	D	E	F
THF/NMP	25	25	24	26
THF	27	37	20	25
Et$_2$O	60	19	12	12
Et$_2$O (reflux)	69	18	9	8

Hayashi, T. et. al. *Org. Lett.* 2004, *6*, 1297.
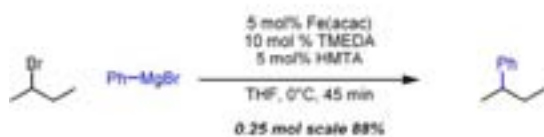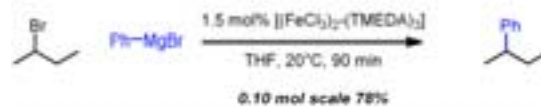
Amines, Particularly TMEDA are Key Additives

Nakamura, E. et. al. *J. Am. Chem. Soc.* 2004, *126*, 3686.

1st Generation:
Stoichiometric TMEDA as additive
8g of product at 90% Isolated Yield

2nd Generation: Catalytic in Amine

Catalytic FeCl$_3$/Et$_3$N (or DABCO) works well. As does:

Bedford Chem. Commun., 2005, 4161 Cahiez et al., Angew. Chem. Int. Ed. 2007, 46, 4364

Substrate scope

Kumada Type Coupling (using TMEDA as ligand)

$$\text{AlkylX} \xrightarrow[\text{THF } 0^\circ\text{C (30min)}]{\substack{\text{FeCl}_3 + \text{TMEDA (5 mole\%)} \\ \text{ArMgBr (1.2 eq.)}}} \text{Alkyl-Ar}$$

Negishi type Couplings (aryl Zinc and Alkyl-Iodides made in-situ from ArMgBr and ZnI$_2$)
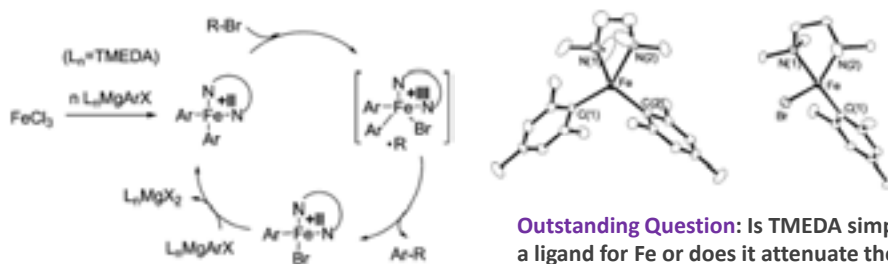

*E. And M. Nakamura Org. Lett., Vol. 11, **2009,** Pg 4306*

Mechanism and Role of TMEDA

Radical Rebound Mechanism (Fürstner/Bedford/Nakamura amongst others)
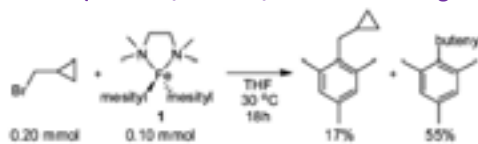
An Fe^{II}/Fe^{III} cycle?

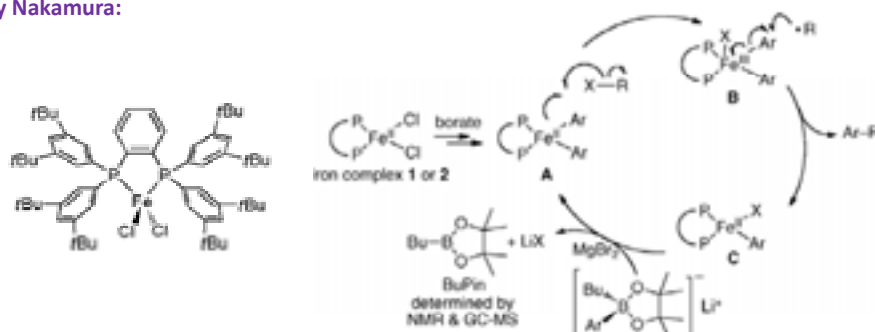**Outstanding Question:** Is TMEDA simply a ligand for Fe or does it attenuate the reactivity of RMgBr as well?

H. Nagashima and M. Nakamura J. AM. CHEM. SOC. 2009, *131, 6078–6079*

11

An Fe Analogue of Suzuki Miyaura Coupling?

Key Catalysts Requirements Defined by Nakamura: Fe(II) Oxidation state, coordinatively unsaturated, significant spin density on Fe.

Beyond TMEDA: (TMEDA)FeCl$_2$ no coupling activity

RLi Base /MgBr$_2$ essential for transmetallation. KF, K$_3$PO$_4$, KOt-Bu, and Cs$_2$CO$_3$ ineffective

Fe-OR/ Fe-F too strong? (diphosphine)FeF$_2$ and (diphosphine)Fe(OEt)$_2$ inactive

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M. Nakamura et al., J. AM. CHEM. SOC. 2010, *132, 10674*

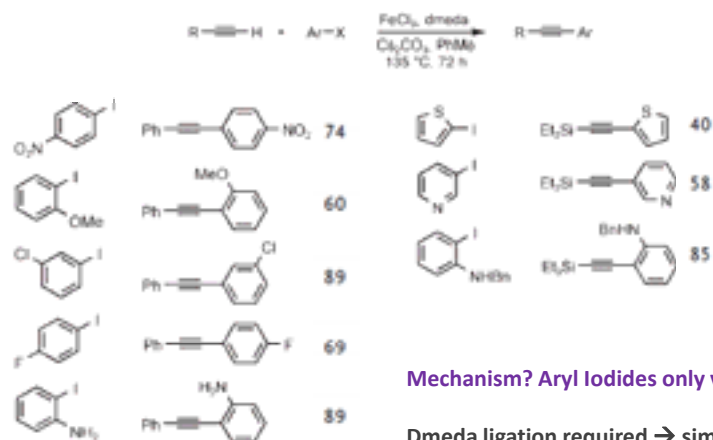## Substrate scope – Fe Catalysed. Suzuki Miyaura

Is this really a Fe Suzuki Miyaura Analogue?
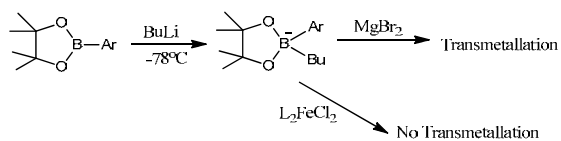
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Fe Catalysed sp-sp² Sonogashira Coupling?

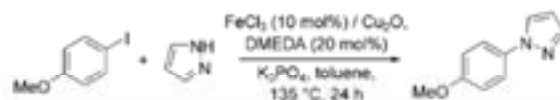**An Iron analogue of the Sonogashira Reaction was also recently reported**

Mechanism? Aryl Iodides only viable

Dmeda ligation required → similar to Cu catalysts in Cu catalysed Sonogashira Reactions

Bolm et al., Angew. Chem. Int. Ed. 2008, 47, 4862

A Note of Caution!! Highly Active Trace Impurities

$FeCl_3/Cu_2O$	Yield [%] (GC)
>98% (Merck)	87 (ref. [3a])
>98% (Aldrich)	26
>99.99 (Aldrich)	9
>99.99% + 5 ppm Cu_2O	78
>99.99% + 10 ppm Cu_2O	79
no Fe + ligand + 5 ppm Cu_2O	77
no Fe + no ligand + 5 ppm Cu_2O	23

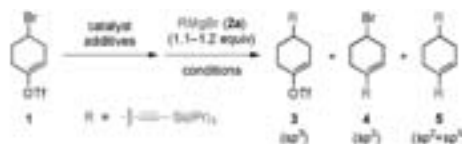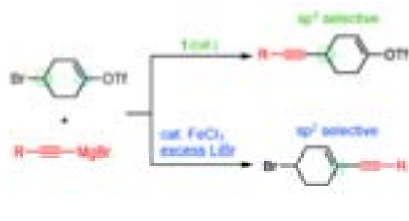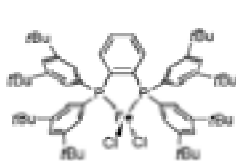[a] DMEDA = N,N-Dimethylethylenediamine.

Rule of Thumb:

If an Fe complex is the active catalyst expect to observe different reactivity patterns, selectivities and/or require different ligands/solvents *etc* compared to Cu/Pd systems.

Bolm/Buchwald ACIE. 2009, 48, 5586 and Norrby /Bolm et al., ACIE 2009, 48, 5691

A 'True' Fe Catalysed Sonogashira Reaction
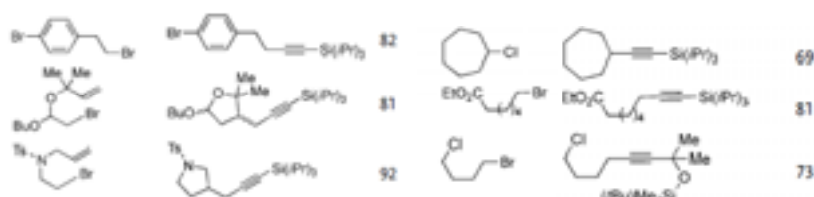
Bulky diphosphine is essential

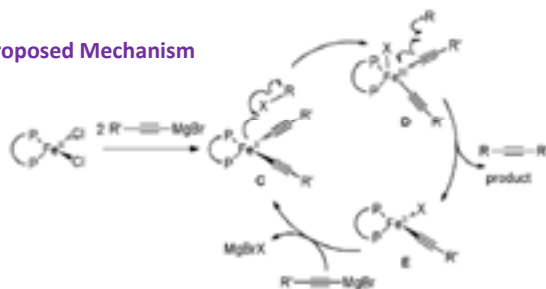

Radical Mechanism

'Ferrates'

M. Nakamura Angew. Chem. Int. Ed. 2011, 50, 10973 −10976

Fe Catalysed sp-sp^3 Songashira Coupling

The Fe catalyst is highly chemoselective for sp^{3}C-X → radical FeII/FeIII cycle
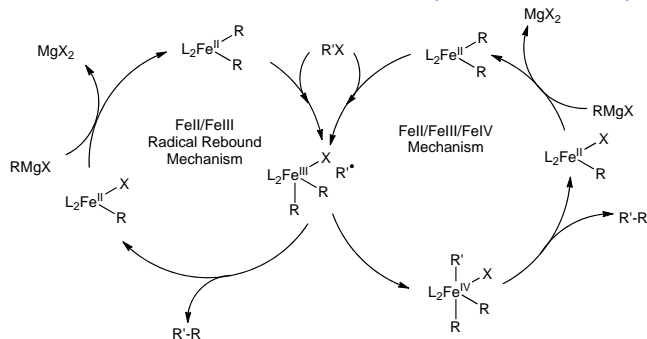

Proposed Mechanism

M. Nakamura Angew. Chem. Int. Ed. 2011, 50, 10973 −10976

FeII/FeIII or FeIV mechanisms?

Both are feasible - oxidative addition can be a two step radical mediated process

There are other outstanding questions:

e.g., Why is Fe cross coupling limited to certain nucleophiles / additives? Grignards seems special?
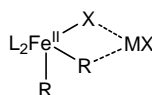
Assist Transmetallation OR generates a more electron rich metal centre for FeII/FeIII?

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The Fluoride Effect - A real FeIV intermediate?

Fe Systems discussed so far were poor catalysts for wide scope aryl-aryl coupling
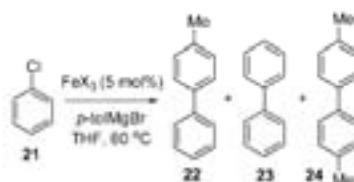
Effective Suppression of HomoCoupling

N-Heterocyclic Carbene Ligand and Fluoride Anion are essential
A range of phosphines and / or Chloride Precursors = ineffective catalysts

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Nakamura *et al.,* JACS. 2007, 129, 9844, and JACS 2009, *131, 11949–11963*

Mechanism

F⁻ binding to Fe prevents over alkylation and reduction – Precludes Low Valent Mechanisms

Substrate Scope
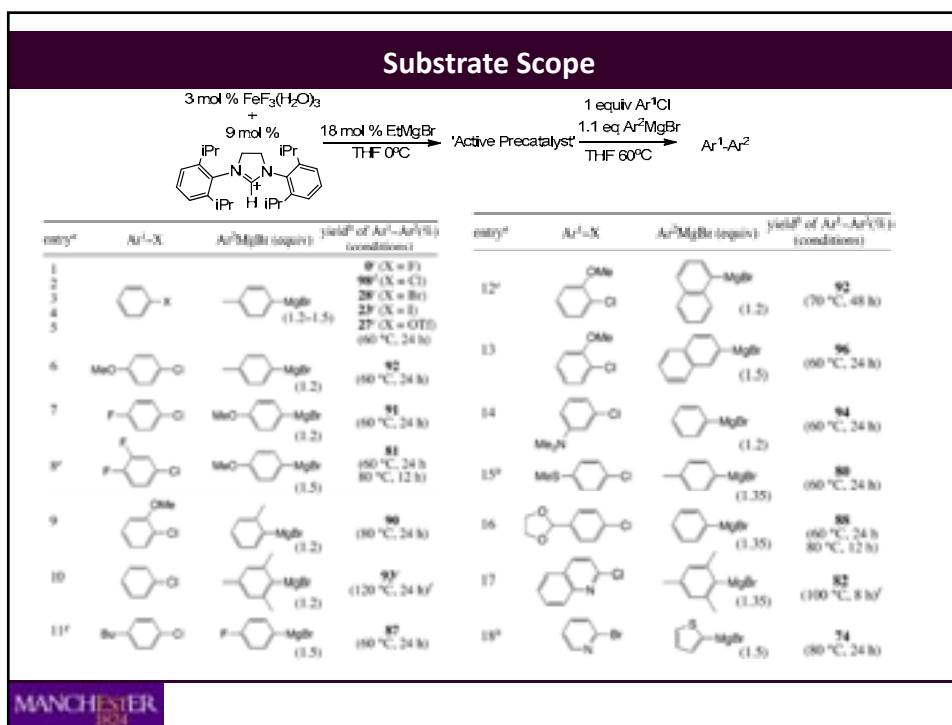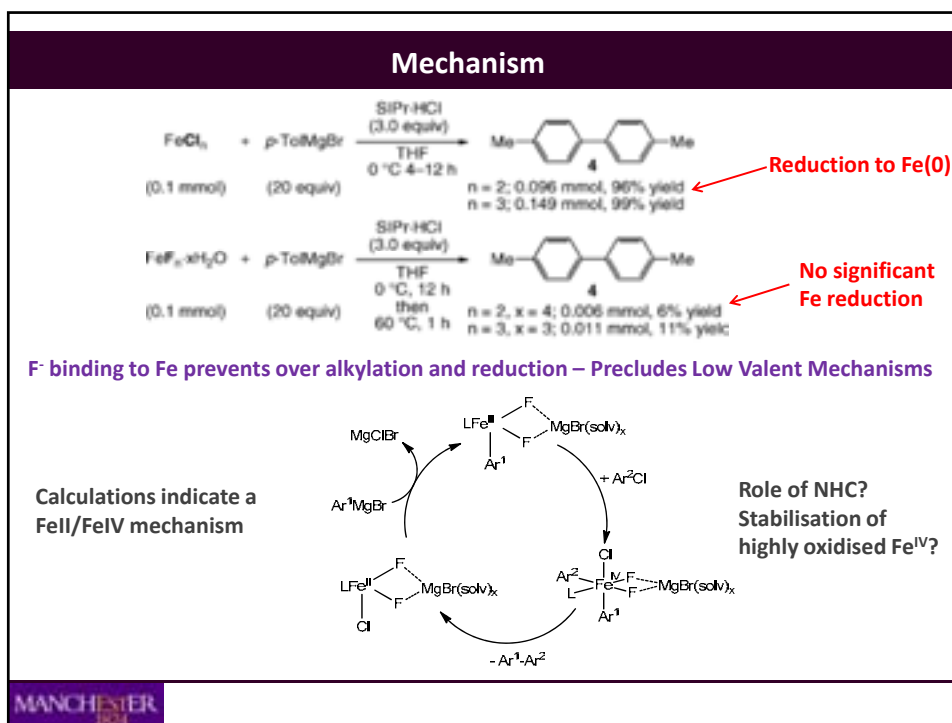
Conclusions Part 1- Cheap metal for a noble task

Fe catalysts can emulate Pd/Ni in numerous cases – <u>with inexpensive ligands</u>

Particularly effective for activation of aryl chlorides and 1º and <u>2º alkyl C-X bonds</u>,

Cross Coupling can be very rapid → ester groups are now compatible

<u>Drawbacks:</u> Can be less general than Pd/Ni catalysis. Still Mechanistic Uncertainty. Seemingly Restricted to Grignard reagents as nucleophiles.

A short Part 2: Where Next for Fe catalysed C-C Coupling:

1) Stereoselective Coupling (e.g., Knochel - Angew. Chem. Int. Ed. 2011, 50, 3303)

2) Sequential Catalysis : Coupling and then … (e.g., cyclisation + cross coupling)
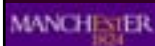
<u>3) Catalytic C-H activation: e.g., Direct Arylation without directing groups</u>

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2. Sequential (Domino) Catalysis

0) Cyclisation and Cross coupling

1) Aryl-Halide Alkyl Halide One-Pot Coupling

Von Wangelin et al., Angew. Chem. Int. Ed. 2009, 48, 607

FeCl$_2$ catalyses Grignard formation and cross coupling
Low [conc] of Grignard – safety benefits
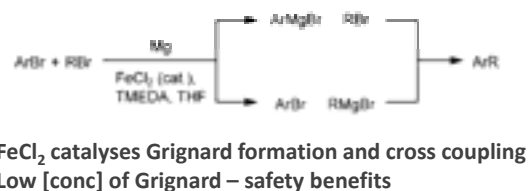
2) Formal sp^3-sp^3 coupling. High Yielding with Li[H$_3$BNMe$_2$] as hydride source
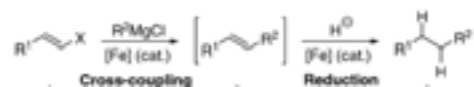
*S. Thomas et al., **Chem. Commun.**, **DOI:** 10.1039/C1CC14622J*

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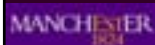
3. C-H Activation : with a Directing Group

cat. Fe(acac)₃/1,10-phenanthroline
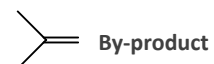ZnCl₂·TMEDA + 2PhMgBr

THF, 0 °C
99%
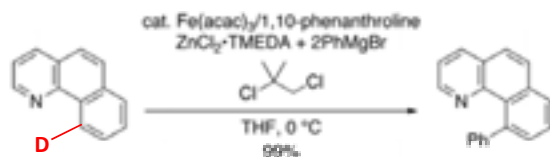
Applicable to phenylated pyridyls, pyrazoles, pyrimidines, quinolines

Mechanism?

1 eq. PhMgBr → Ph-**D**

NN ligands and Mg essential.
Fe^{II} and Fe^{III} sources are identical

By-product

O$_2$ not efficient (yields ~ 20 %)

Fe(acac)₃ (10 mol %)
dtbpy (15 mol %)   PhMgBr (3 equiv)

Cl⌃Cl (2 equiv)   0 °C, 5 min

solvent = PhCl/THF   99% (E/Z = < 1:99)
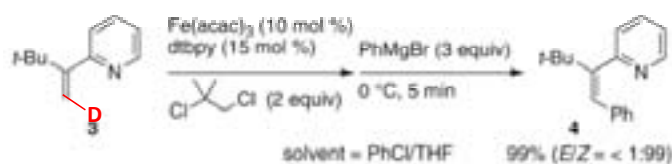
No alkene Reduction, with cyclohexene-pyridyl no other olefin regioisomers

MANCHESTER E. Nakamura et al., J. AM. CHEM. SOC. 2008, *130, 5858 and* 2011, 133, 7672

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3. Direct Arylation with <u>No Directing Group</u>.

FeCl₃ (15 mol %)
DMEDA (30 mol %)
80 °C
48 h
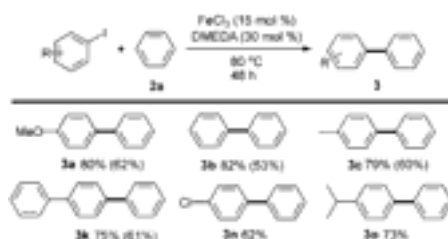
Aiwen Lei et al., Angew. Chem. Int. Ed. 2010, 49, Pg 2004.
Fe(III) Precursor

3a 60% (62%)   3b 62% (53%)   3c 79% (60%)

3k 75% (61%)   3n 62%   3e 73%

Concurrently: Fe(II)

Fe(OAc)₂ (5 mol %)
bathophenanthroline (10 mol %)
KOt-Bu (2 equiv)

80 °C, 20 h

72 %   **69 %**   **40%**   **86%**   **85%**   **79%**
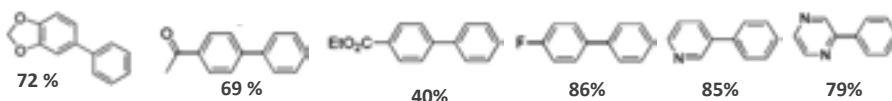
MANCHESTER   Charette et al., J. AM. CHEM. SOC. 2010, *132, 1514*

3. C-H Activation : Direct Arylation

Definitively not Cu catalysed.

entry	catalyst	purity (%)	commercial source	yield
1	Fe(OAc)$_2$	99.995	Aldrich	98 (87)
2	Fe(OAc)$_2$	97	Strem	91
3	Cu(OAc)	99	Strem	6
4	Cu(OAc)$_2$	97	Strem	9
5	Fe(OAc)$_2$ + Cu(OAc)	99.995 + 99	Aldrich Strem	57
6	Fe(OAc)$_2$ + Cu(OAc)$_2$	99.995 + 97	Aldrich Strem	48

Mechanistic Studies:

Kinectic Isotope Effect = 1.04

Radical Mediated Reaction

No Scavenger = 91% (GC)
TEMPO = <1% (GC)
Galvinoxyl = <1% (GC)

entry	catalyst	ligand	KOt-Bu	yield (%)
1	Fe(OAc)$_2$	10 mol %	2 equiv	91
2	none	10 mol %	2 equiv	0
3	AIBN	none	2 equiv	17
4	Fe(OAc)$_2$ + AIBN	10 mol %	none	0

Charette et al., J. AM. CHEM. SOC. 2010, *132*, *1514*

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3. C-H Activation : Direct Arylation

Use of toluene :
Regiochemistry (high ortho) supports Homolytic Aromatic Substitution (H.A.S.)

Drawback :
1 equivalent of the aryl iodide but
100 equivalents of the arene required!

Proposed HAS Mechanism

Oxidation State of Fe?

Other Observations
tBuOK essential. tBuOH
observed (Sequester HI by-
product)

Similar Initiation Step to Mechanism found
in ATRP by Iron (II) catalysts.

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Extension to sp³ C-H Activation : albeit with a Directing Group

FeII/FeIII precursors identical outcomes

91 (X = H)
91 (X = F)
88 (X = Cl)
90 (X = OMe)

54

70

69

(74)

Indolines, pyrroles, anilines, 2-
pyrrolidones – not viable
substrates – Reduction of C-I to
C-H

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E. Nakamura   J. AM. CHEM. SOC. 2010, *132, 5568*

Certainly a believer in the Iron Age

Particularly useful for:

1)Coupling of Aryl-Cl using cheap ligands extremely rapidly (even at low temperatures)
2) Different Functional Group Tolerance (Aryl-I, Aryl Br compatible)
3) Radical reactions especially sp^3-C-X activation and coupling

The future - Radical C-H based functionalisation? Other (less hazardous) Nucleophiles ?
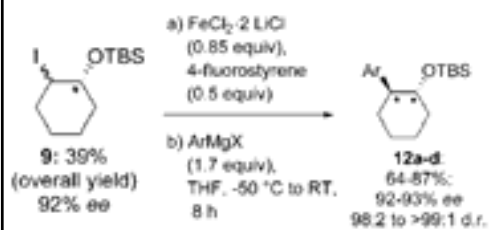

Reviews in this area:

1)   Overview of Fe Catalysis (as 2008):
         Iron Catalysis in Organic Synthesis (WILEY-VCH)

2)   Fe Cross coupling
       Acc. Chem. Res. 2008, 41, 1500.
       ChemSusChem 2009, 2, 396 – 417
       Chem. Soc. Rev., 2008, 37, 1108

3)   Alkyl-Organometallics in Cross Coupling
       Chem. Rev 2011, 111, 1417,

4)   Fe Catalysts for Direct C-H Transformation
       Chem. Rev. 2011, 111, 1293–1314

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