Iron Catalysed Coupling Reactions

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Fe $[\text{Ar}]3d^64s^2$

The fourth most common element in the Earth's crust

Relatively less understanding and manipulation of the reactivities of organoiron species
Before the era of “coupling reactions”

Radical couplings were intensively studied, some of which are initiated by iron.

Such a concept led to a great discovery.

Before the era of “coupling reactions”

Besides homocoupling of Grignard reagents, Kharasch et al. disclosed a cross coupling reaction between Grignard reagents and aryl halides

\[
egin{align*}
\text{Br} & \quad + \quad \text{MgBr} \\
\text{FeCl}_3 \text{ (5 mol\%)} & \quad \text{THF} \\
\end{align*}
\]

47%

*J. Am. Chem. Soc.*, 1941, 2316

It’s a pity that this discovery didn’t start the modern coupling reaction field. Chemists didn’t pay much attention to coupling reaction until 30 years later.
Genesis

Renaissance of coupling reactions since 1970’s

Iron catalysis is among the first published examples under the modern coupling concept

Koich et al. discovered this highly efficient cross coupling at low temperature and low catalyst loading (~ 0.1%), highlighted by retented stereochemistry.

Proposed mechanism

“Soluble reduced iron” was proposed

Renaissance of coupling reactions since 1970’s

With the formulation of the “oxidative addition”, “transmetallation” and “reductive elimination” concepts, Fe(I)/Fe(III) mechanism was proposed by Kochi et al.

\[ \text{Grignard reagent} \rightarrow \text{Fe(III)} \rightarrow \text{Fe(I)} \rightarrow \text{Me} = \text{Fe}^{\text{III}} \rightarrow \text{Me} = \text{R} \rightarrow \text{MgBrX} \rightarrow \text{RMgBr} \]

Organomagnesium Nucleophiles (Kumada Couplings)

Set off from vinyl electrophiles

Following the first success by Kochi et al., various vinyl electrophiles were made available for iron catalyzed Kumada couplings.

\[
\text{PhMgBr} + \quad \text{Ph} \quad \xrightarrow{\text{Fe(DMB)}_3 \text{ (1 mol\%)} \atop \text{DME, -20 °C-rt} \atop 2 \text{h}}} \quad \text{Me} \quad \text{Ph} \quad 68\% \\
\]


\[
\text{OctMgBr} + \quad \text{Me} \quad \xrightarrow{\text{FeCl}_3 \text{ (3 mol\%)} \atop \text{NMP (9 eq.)}} \quad \text{Me} \quad \text{Oct} \quad 88\% \\
\]

Cahiez et al., *Synthesis*, 1998, 1199

NMP as “co-solvent”, or precisely ligand is one of the most important discovery in this transformation in 1990’s, which makes several other electrophiles to be available.
Organomagnesium Nucleophiles (Kumada Couplings)

Set off from vinyl electrophiles

\[
\text{MeO} \quad \text{MgBr} + \quad \text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{MgBr} + \quad \text{TfO} \quad \text{MeO} \\
\text{BuMgBr} + \quad \text{Ph} \quad \text{Bu} \\
\]

Itami et al., Org. Lett., 2005, 1219


Cahiez et al., Synthesis, 1998, 1199
Aryl electrophiles

The first systematic study on such coupling reactions with aryl electrophiles was published by Fürstner et al. in 2002.

- Best leaving groups: Cl⁻, OTf⁻ and OTs⁻, but Br⁻ and I⁻ are not good leaving groups
- Heterocycles as well as some nucleophilic functional groups are tolerated
- Primary alkyl Grignard reagents are main nucleophiles while Fe(salen)Cl is effective for secondary nucleophiles
- Softer nucleophiles such as organozinc and organomanganese reagents are effective

Organomagnesium Nucleophiles (Kumada Couplings)

Aryl electrophiles

A hypothesized mechanism
Aryl electrophiles

More interestingly, controlled alkylation can be achieved by different leaving groups

Organomagnesium Nucleophiles (Kumada Couplings)

Aryl electrophiles

A coupling starting from aryl ammonium salts was disclosed by Wang et al. in 2013

\[
\text{Fe(acac)}_3 (10 \text{ mol%}) \quad \text{THF/NMP (7/1), rt, 1 h, 95%}
\]

Zhong-Xia Wang et al., *Tetrahedron*, 2013, 9580

Malhotra et al. reported a study on reactivity control using ligand on aromatic rings

\[
\text{Fe(acac)}_3 (3.75 \text{ mol%}) \quad \text{THF, MeMgBr} \quad \text{84% yield}
\]

Malhotra et al., *Org. Lett.*, 2013, 3698
Aryl electrophiles

NHC ligands can further increase electrophile scope

\[
\text{Me}_2\text{N}^+\text{SO}_2^\text{Me}_2\text{N} + \text{Me}_2\text{NO}^+\text{CO}_2^\text{Me}_2\text{NO}
\overset{\text{alkylMgBr}}{\xrightarrow{\text{FeCl}_2 (5 \text{ mol\%}) \text{, Ligand (20 \text{ mol\%})}}}
\text{alkyl}
\]

DCM/THF, 65 °C

**Organomagnesium Nucleophiles (Kumada Couplings)**

**Alkyl electrophiles**

The wide use of alkyl nucleophiles shed light on the intrinsic advantage of iron to tolerate alkyl coupling partners. Coupling starting from alkyl electrophiles is also realized.

\[
\begin{align*}
\text{Br} & \quad \text{FeCl}_3 (5 \text{ mol}\%) \\
\text{TMEDA} (1.2 \text{ eq.}) & \quad \text{PhMgBr} (1.2 \text{ eq.}) \\
\text{THF,} & \quad -78 \, ^\circ\text{C to } 0 \, ^\circ\text{C, 30 min} \\
\text{Br} & \quad \text{Ph} \\
71\% & \quad 19\% & \quad 3\% & \quad 10\%
\end{align*}
\]


\[
\begin{align*}
\text{Br} & \quad \text{MgBr} \\
\text{Fe(acac)}_3 (5 \text{ mol}\%) & \quad \text{ether, reflux, 30 min} \\
\text{73}\%
\end{align*}
\]

**Organomagnesium Nucleophiles (Kumada Couplings)**

### Alkyl electrophiles

The wide use of alkyl nucleophiles shed light on the intrinsic advantage of iron to tolerate alkyl coupling partners. Coupling starting from alkyl electrophiles is also realized.


**Hayashi et al., Org. Lett., 2004, 1297**
Organomagnesium Nucleophiles (Kumada Couplings)

Alkyl electrophiles

Driven by Fe(-II) active catalyst hypothesis, Fürstner et al. reported an alkyl-aryl coupling reaction with a well defined Fe(-II) complex.

\[
\text{Br-C}_7H_8 + \text{MgBr} \xrightarrow{[\text{Li(tmeda)}]_2[\text{Fe(C}_2\text{H}_4)_4]} \text{THF, -20º C} \rightarrow \text{Cy-C}_7H_8, 94\%
\]


A radical mechanism was proposed.
Alkyl electrophiles

Denmark et al. systematically studied coupling reactions with sulfur containing electrophiles, in which iron catalysts were also explored.

Denmark et al., J. Org. Chem, 2013, 12593
**Organomagnesium Nucleophiles (Kumada Couplings)**

**Alkyl electrophiles**

Later on, the catalyst system with catalytic amount of amine ligand was developed.

\[
\text{MgBr} + \text{Br} \rightarrow \text{Fe(acac)}_3 (5 \text{ mol\%}) \quad \text{TMEDA} (10 \text{ mol\%}) \quad \text{HMTA} (5 \text{ mol\%})
\]

THF, 0º C, 45 min

![HexaMethyleneTetraAmine](image)

92%


The first time when HMTA was reported to be applied to transition metal catalysis

For other ligand study, see Bedford *et al.*, Chem. Commun., 2005, 4161
M. Nakamura et al. reported a coupling reaction with bulky alkyl group.

M. Nakamura et al., Chem. Lett., 2011, 1030
Alkyl electrophiles

M. Nakamura *et al.* reported a coupling reaction with bulky alkyl group.

\[
\text{[Fe}^{II}] \text{ (3 mol%)}
\]

\[
\text{Ligand (3 mol%)}
\]

\[
\text{THF, 0\degree C}
\]

\[
\text{MesMgBr}
\]

\[
\text{slow addition 40\degree C, 3h}
\]

\[
\text{74%}
\]

A radical species was generated.

Organomagnesium Nucleophiles (Kumada Couplings)

Alkyl electrophiles

Coupling reactions involving vinyl and alkyl nucleophiles were also achieved.


Cahiez et al., Org. Lett., 2007, 3253
Alkyl electrophiles

Chai et al. reported the first alkyl-alkyl coupling.

\[
\text{Br} \quad \text{Fe(OAc)}_2 \text{ (3 mol\%)} \quad \text{nBuMgBr} \\
\text{Xantphos (6 mol\%)} \quad \text{ether, rt, 15 min} \quad \text{nBu} \\
\]

64%

Softer Nuleophiles

Organozinc nucleophiles

The 2002 Angewandte paper from the Fürstner lab sheds light on the possibility to apply organozinc and organomagnesene nucleophiles.

Nakamura and coworkers showed an efficient Negishi coupling in 2005.

\[
\begin{align*}
\text{FeCl}_3 \text{ (5 mol\%)} & \quad \text{TMEDA (1.5 eq.)} \\
\text{ZnCl}_2/\text{PhMgBr (1/2)} & \quad \text{THF}, \\
50 \degree \text{C, 30 min} & \quad \text{96\%}
\end{align*}
\]

Nakamura et al., Synlett., 2005, 1794

Bedford and coworkers showed an iron phosphine catalyst in 2009.

Bedford et al., Chem. Commun., 2009, 600
**Softer Nucleophiles**

**Organozinc nucleophiles**

\[ \text{FeCl}_3 \text{ (5 mol\%)} \]
\[ \text{TMEDA (1.5 eq.)} \]
\[ \text{ZnCl}_2/\text{PhMgBr (1/2)} \]

\[ \text{THF, 50 }^\circ\text{C, 30 min} \]

Nakamura *et al.*, *Synlett.*, **2005**, 1794


Magnesium salt was shown to be critical for this transformation.

\[ \text{R}_2\text{Zn} + \text{MgX}_2 \rightleftharpoons \text{RZnX} + \text{RMgX} \]

It was proposed that the Grignard reagent formed *in situ* by hetero-Schlenk equilibrium plays an important role in this reaction.
Organoboron nucleophiles are shown to be more challenging, perhaps due to Fe/B transmetallation difficulties.

Bedford and coworker introduced tetraarylborates into the reaction and realized the coupling reaction with moderate yield.

\[
\text{Bedford et al., Chem. Commun., 2009, 600}
\]

There are also cases showing inorganic zinc salts can serve as co-catalyst in the Suzuki type coupling.

Coupling reactions with aryloborates and vinyl borates were achieved by M. Nakamura. See his 2010 papers.
**Other Nucleophiles**

- Organolithium nucleophiles are among the strongest nucleophiles. Nonetheless, coupling reactions with organolithium nucleophiles remains challenging. There is a successful case using TMEDA as ligand, see Wong et al., 10.1038/ncomms10614

- Bedford and coworkers also tried organoaluminum, organogallium, organoindium and organothallium nucleophiles with success. See *Organometallics*, 2014, 5767
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