Domino Reactions

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From Oblivion into the Limelight: Iron (Domino) Catalysis

*Alois Fürstner**

catalysis · cross-coupling · domino reactions ·
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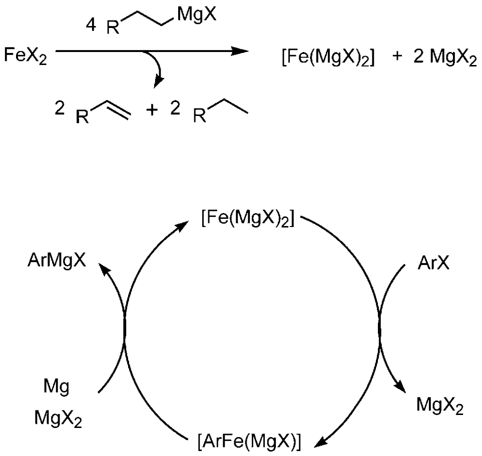
Iron is one of the few remaining niches in the Periodic Table of the Elements as far as applications in homogeneous catalysis are concerned. Located above ruthenium as one of the most versatile central metals in the arsenal, iron is cheap, nontoxic, benign, readily available, rich in oxidation states, and amenable to ligation to equally inexpensive (nitrogen- or oxygen-based) ligand sets. It serves nature as/in the operational unit of many biological catalysts (cytochrome P450, nitrogenase, methane monooxygenase etc) to effect some of the most difficult chemical transformations with admirable ease.[1] Despite these many advantageous attributes, iron-based catalysts are still surprisingly underrepresented in the field of organic synthesis.[2]

A string of remarkable recent publications, however, may indicate that this situation is about to change. The desire to emulate iron-catalyzed biological processes in the test-tube constitutes one important source of inspiration; another is older literature, where observations are buried that may not have been fully appreciated at the time they were published but now re-surface in an attractive format. A good example is the recent publication by Jacobi von Wangelin and co-workers, who describe a magnesium-mediated direct cross-coupling reaction between aryl halides and alkyl halides, in which an iron catalyst plays two roles in succession.[3] This study nicely integrates several previously available pieces of information on iron catalysis into what seems to be a highly practical method.

The profound, but somewhat alchemistic, influence of metal impurities, in particular traces of iron, in the magnesium used for the preparation of Grignard reagents was already noted in the early literature.[4] Yet, it was not until the turn of the century that Bogdanović and Schwickardi managed to make use of this effect.[5] Specifically, they showed that $FeCl_2$ (2 mol %) effectively catalyzes the formation of the C–Mg bond, most likely by intervention of a highly reduced intermetallic cluster with the formal composition $[\{Fe(MgCl)_2\}_n]$ that is generated in situ (Scheme 1). This process is fundamentally different from the common practice to entrain Grignard reactions by etching the passivated surface of the magnesium turnings with appropriate additives. Rather, it is the low-valent iron species that primarily inserts into the carbon–halogen bond, followed by an unconventional reductive elimination of the resulting organoiron intermediate that releases the desired Grignard reagent. The ensuing catalytic cycle is powerful, as it allows the generation of organomagnesium compounds even from deactivated aryl chlorides, which generally do not react (Scheme 1).[5]



Scheme 1. Mechanism for the formation of a low-valent intermetallic iron–magnesium cluster and its role as the catalyst for the formation of Grignard reagents, as proposed by Bogdanović and Schwickardi.[5] X = halogen.

Shortly thereafter, our research group proposed that the very same low-valent iron clusters might also serve as catalysts for C–C bond formations.[6] Following up on pioneering studies by Tamura and Kochi on iron-catalyzed cross-coupling reactions of alkenyl halides with Grignard reagents,[7] we were able to demonstrate that aryl chlorides, triflates, and even certain tosylates are amenable to iron-catalyzed cross-coupling reactions, again possibly through the intervention of $[\{Fe(MgCl)_2\}_n]$ as the catalytically competent species (Scheme 2).[6] Although this process is not (yet) as general as its palladium-catalyzed counterparts, many such reactions proceed with excellent yields and unprecedentedly high rates under notably mild conditions, and are readily amenable to scale-up.[8] Moreover, they tolerate a host of polar functional groups that would normally react with a Grignard reagent. Sequential iron-catalyzed cross-coupling reactions of difunctional substrates, performed in one pot

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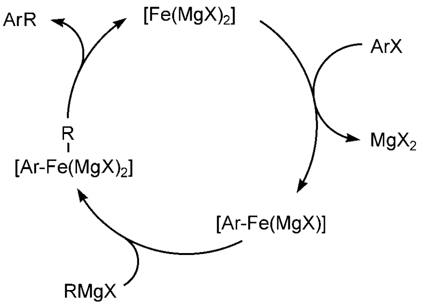
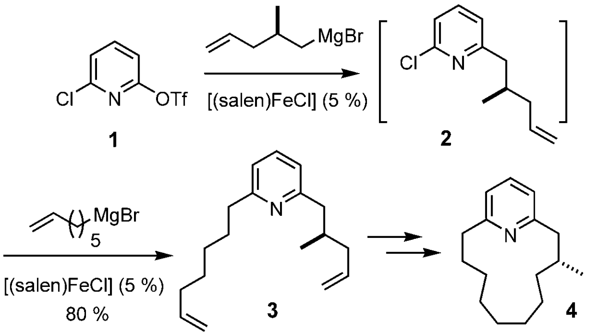
[*] Prof. A. Fürstner
Max-Planck-Institut für Kohlenforschung
45470 Mülheim/Ruhr (Germany)
Fax: (+49) 208-306-2994
E-mail: fuerstner@mpi-muelheim.mpg.de



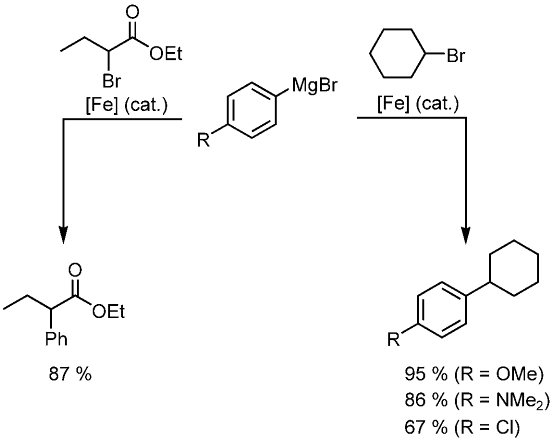
Scheme 2. One of the conceived scenarios for the iron-catalyzed cross-coupling reactions of aryl halides (triflates) ArX with alkyl-Grignard reagents as proposed by Fürstner et al.[6,15]

without the need to purify the intermediates, have also been described by using this method (Scheme 3).[9]



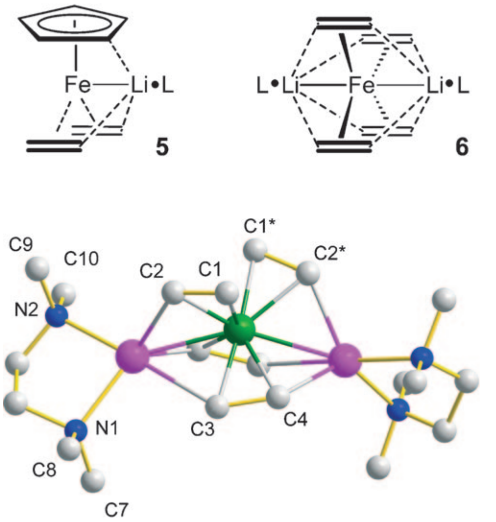
Scheme 3. Sequential cross-coupling reactions of two different alkylmagnesium halides with a difunctional aromatic substrate as one of the key steps in a synthesis of muscopyridine (**4**).[9] Salen = *N*,*N*′-bis(salicylidene)ethylenediamine.

Since then, many research groups have helped increase the scope of iron-catalyzed cross-coupling reactions even further.[10] A particularly noteworthy development was the finding that C–C-bond formation can also be effected by inverting the polarity of the reaction partners. Whereas the coupling of an aryl halide ArX with an alkyl-Grignard reagent RMgX mimics the conventional logic of palladium and nickel catalysis, it was independently shown by four research teams that the same type of products can also be obtained by reaction of arylmagnesium halides ArMgX with *alkyl* electrophiles RX (Scheme 4).[11,12,15] Alkyl halides are challenging substrates because of their high barrier to oxidative addition and the proclivity of the once-formed alkyl–metal complexes towards β-hydride elimination.[13] Therefore, it is surprising how willingly they succumb to cross-coupling reactions in the presence of simple iron catalysts.[11,12,15]



Scheme 4. Selected examples of cross-coupling reactions of arylmagnesium halides with alkyl electrophiles. Such transformations can be catalyzed by low-valent iron species prepared ex situ[12,15] as well as in situ.[11]

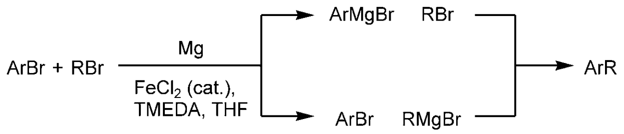
These advances notwithstanding, iron catalysis does not yet have any firm conceptual framework, not least because sound mechanistic information is scarce. However, a recent study into this largely void terrain demonstrated that iron-catalyzed C–C bond formations fall into (at least) two distinct categories. In certain cases iron-ate complexes are operative;[14,15] however, if the R group delivered by RMgX can undergo β-hydride elimination after transmetalation to iron, low-valent species are generated, as originally proposed by Bogdanović and Schwickardi.[5] Even though these catalysts are only metastable and very difficult to characterize, their structure and reactivity can be emulated by well-defined intermetallic iron complexes such as **5** or **6** (Scheme 5).[15]



Scheme 5. Top: Lithium iron-ate complexes **5** and **6** (L = TMEDA) which were used to emulate the behavior of the low-valent iron catalysts generated in situ. Bottom: Structure of **6** in the solid state, revealing the short intermetallic contacts between the lithium (pink) and iron centers (green).[15]

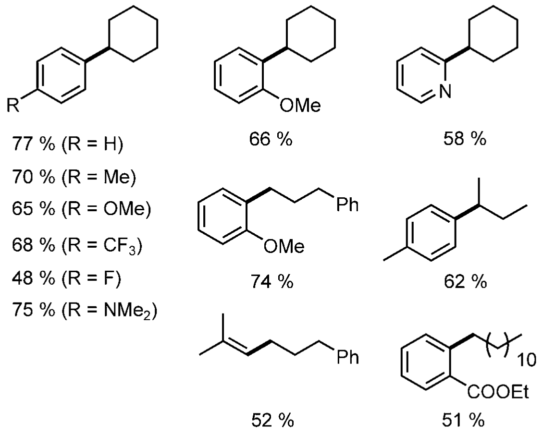
Their iron centers exhibit low formal oxidation states (0 or −II), are engaged in fairly covalent bonding with the escorting lithium cations, and are ligated by kinetically labile ethylene units. Such complexes undergo oxidative insertion into aromatic, allylic, benzylic, and aliphatic halides, as shown unequivocally by isolation of the resulting unstabilized organoiron species.[15] Since **5** and **6** serve as powerful precatalysts for cross-coupling experiments of all kinds, they represent structural as well as functional surrogates of intermetallic clusters of type [{Fe(MgCl)$_2$}$_n$], which are presumed to be operative under the "in situ" conditions.[12,15]

Jacobi von Wangelin and co-workers have now merged this prior knowledge into a highly practical protocol.[3] They showed that the formation of a Grignard reagent and its cross-coupling reaction with a suitable partner need not be carried out in two consecutive steps, but can be integrated into a user-friendly one-pot procedure. Thus, reaction of a mixture of an aryl bromide ArBr and an alkyl bromide RBr (1.2 equiv) with a suspension of magnesium in THF at 0°C to ambient temperature delivers the corresponding cross-coupling product ArR in moderate to good yields, provided that catalytic amounts of FeCl$_2$ and excess *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) are present in the mixture. The homocoupling of the individual partners was barely observed (<9% of Ar–Ar was detected in the cases investigated; Scheme 6).[3] It is believed that the in situ generated [{Fe(MgCl)$_2$}$_n$] initially effects formation of the Grignard reagent, which is then rapidly consumed by the ensuing cross-coupling reaction with the admixed electrophilic partner, also effected by the very same catalyst. Thus, the low-valent iron powers two different elementary steps in a well-synchronized domino process.



Scheme 6. Iron-catalyzed direct cross-coupling reaction of aryl and alkyl bromides.[3]

The scope of this new method seems reasonably broad (18 examples, 20–81% yield) and several functional groups were shown to be tolerated (Scheme 7).[3,16] Even though organic bromides tend to give better yields, the corresponding chlorides can also be used under slightly more forcing conditions. What makes the procedure particularly attractive from an application point of view, however, is the fact that there is no build-up of large concentrations of the Grignard reagent, and hence no big exotherms are created; only "steady-state" concentrations of the organometallic compound as low as less than 4% were detected during the course of the reaction.[3] This observation suggests that the formation of the Grignard reagent is the rate-determining step of the entire process, whereas the ensuing cross-coupling reaction occurs rapidly. This conclusion is in line with our own previous findings.[6]



Scheme 7. Selected examples of direct cross-coupling reactions of aryl or alkenyl bromides with alkyl bromides by using the one-pot Mg/FeCl$_2$/TMEDA protocol. The newly formed bond is shown in bold.[3]

One may wonder which of the two organic halides is converted into the magnesium reagent and which one serves as the electrophile. The data provided by Jacobi von Wangelin actually suggest that both possible Grignard reagents do form in situ, with the consumption of the alkyl bromide being only slightly faster.[3] This competition, however, is inconsequential, as iron is capable of effecting the cross-coupling of either combination of partners with similar ease (Scheme 6). This striking ability suggests that iron catalysis cannot only serve as a benign and cost-effective substitute for established palladium and nickel chemistry, at least in certain cases, but that the search for reactivity that is unique to this particular element is worthwhile. This quest should clearly extend beyond cross-coupling reactions,[10,17] as iron has also started to find applications in other fields as diverse as hydrogenation and hydrosilylation,[18] cycloisomerization and cycloaddition,[19] CH activation,[20] carbometalation and conjugate additions,[21] as well as oxidation,[22] to name but a few. A sustained development, however, will require much deeper insights into the structure and reactivity of (nonstabilized) organoiron intermediates.[15,23] Even though this constitutes a tremendous challenge, "fundamental insights will almost certainly reward the efforts of the brave".[15]

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