Active Species and Mechanistic Pathways in Iron-Catalyzed C–C Bond Forming Cross-Coupling Reactions

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ABSTRACT. Over the past decade, considerable progress on iron-catalyzed C–C bond forming cross-coupling reactions has been made, leading to the successful development of several new catalytic systems. This perspective presents the proposed mechanistic pathways of iron-mediated cross-coupling reactions of organohalides and Grignard reagents, and discusses the evidence documented in the literature that distinguishes whether such pathways proceed *via* single- or double-electron processes. When cross-coupling reactions are conducted in the presence of ligands, there is still much discussion in the literature as to whether the lowest iron oxidation state responsible for catalytic activity is Fe(I) or Fe(II). However, when ligand-free conditions are employed, it has been shown that iron reaches an Fe(I) oxidation state, allowing an Fe(I)/Fe(III) catalytic cycle. Moreover, for cross-couplings using alkyl halide electrophiles, evidence suggests that the reaction proceeds through single-electron steps, with the generation of

an alkyl radical. While this topic is still the subject of much debate, it is thought that reactions of alkyl Grignards with aryl and alkenyl electrophiles proceed *via* a double-electron pathway.

KEYWORDS. Iron, cross-coupling, oxidation state, Grignard reagents, reaction mechanism.

1. INTRODUCTION

In organic synthesis, transition-metal-catalyzed cross-coupling reactions are among the most used carbon-carbon bond-forming processes.[1] Several catalysts have been successfully developed to mediate such transformations. In particular, palladium- and nickel-based catalysts have been exploited, serving as versatile tools to efficiently forge carbon-carbon bonds.[2] Despite the pivotal role these catalysts play in organic synthesis, the major drawbacks of using such metal catalysts are their high cost, toxicity and relatively low natural abundance. These shortcomings have therefore prompted the development of novel catalysts based on earth-abundant and environmentally sustainable elements.

Unlike palladium or nickel, iron represents an abundant, inexpensive and environmentally friendly alternative. Furthermore, the last fifteen years have experienced a significant increase in interest in the development of iron-catalyzed cross-coupling reactions.[3,4] The study of the mechanistic pathway, as well as the identification of the active iron species involved in these transformations are of primary importance to promote the development of novel transformations whilst pushing the boundaries of the existing reactions. As such, this perspective will take into consideration the active species involved in iron-catalyzed C–C cross-coupling reactions between organohalides with Grignard reagents. Moreover, experimental evidence reported to support single- versus double-electron mechanisms is presented.

2. HISTORICAL BACKGROUND

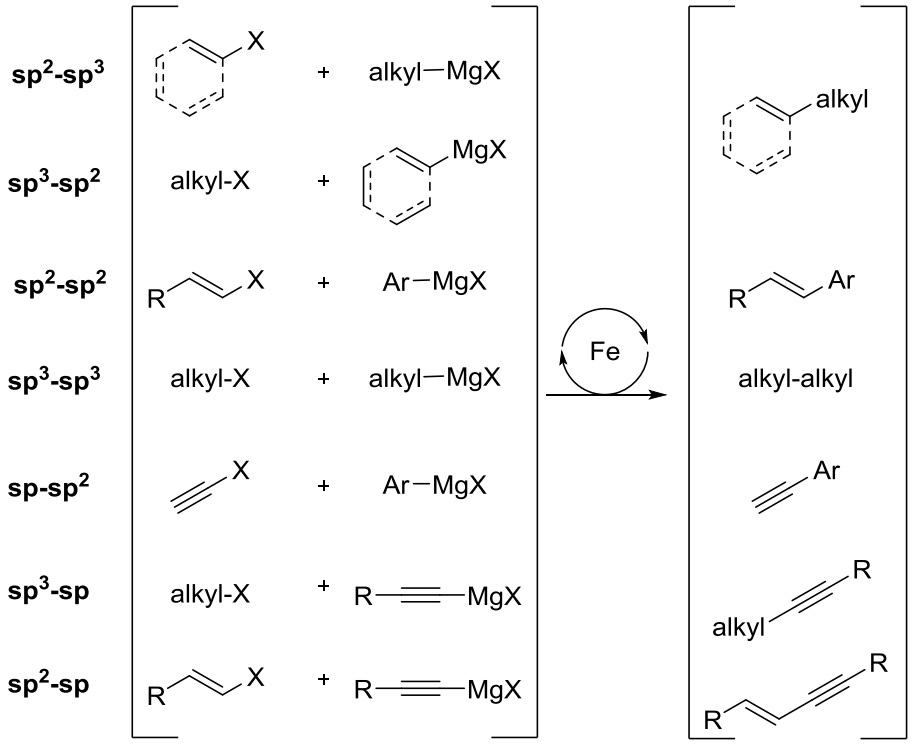
Iron mediated cross-coupling reactions were first described in 1941 by Kharasch and Field in which Grignard reagents were coupled with organohalides in the presence of metallic halides.[5] More specifically, the authors showed that biphenyl was efficiently formed when reacting phenylmagnesium bromide with bromobenzene in the presence $FeCl_3$. A few years later Vavon and Mottez reported the first iron-catalyzed coupling between aryl Grignard reagents and alkyl halides.[6] It is interesting to note that it took another three decades for the next publication on this topic to emerge in the literature, in which Kochi and co-workers described the iron-catalyzed cross-coupling reaction of alkenyl halides with Grignard reagents.[7] Despite these seminal studies, concurrent work lead by the groups of Cahiez[8] and Fürstner,[9] as well as significant contributions from the groups of Nakamura,[10] Hayashi[11] and Bedford[12] in the late `90s and early 2000s, strongly marked the renaissance of iron-catalyzed cross-coupling reactions. Since then, several new iron-catalyzed transformations have been discovered and successfully applied to organic synthesis.[3]

3. SCOPE OF IRON-CATALYZED C–C BOND FORMING CROSS-COUPLING REACTIONS

Iron catalysis has found application in a number of chemical transformations such as addition, substitution, cycloaddition, hydrogenation, reduction, isomerization, rearrangement, polymerization, elimination and oxidation reactions.[3] Furthermore, over the past fifteen years, various iron-catalyzed cross-coupling reactions have been developed. Iron catalysis has proven to be very tolerant towards the nature of both nucleophiles and electrophiles involved in the cross-coupling. Indeed, many different types of organometallic nucleophiles such those based on

Mg, Zn, Cu , Al, B, In, Ga, Ti or Tl have been successfully reacted with a variety of different electrophiles including halides, tosylates, sulphonates, phosphates, carboxylates, selenates and acyl halides.[3] Due to its versatility, iron catalysis has gained much interest amongst the scientific community. The development and gradual refinement of iron-catalyzed C–C bond forming reactions has significantly contributed to key transformations in the total synthesis of complex natural products.[13] Moreover, the development of specific ligands has also allowed the optimization of highly enantioselective transformations.[3p]

In particular, the iron-catalyzed variation of the Kumada–Tamao–Corriu reaction has been thoroughly investigated and its scope expanded to facilitate the coupling between different combinations of sp-, sp^2- and sp^3-hybrized nucleophiles and electrophiles (Scheme 1).[3]

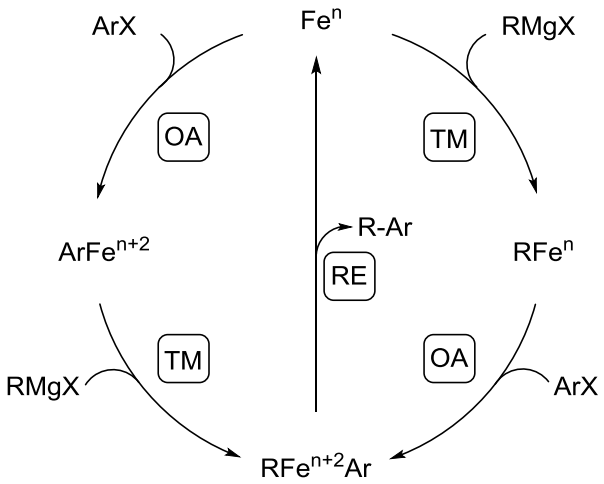


Scheme 1. Examples of iron-catalyzed C–C bond forming cross-coupling reaction between organohalides with Grignard reagents.

4. PROPOSED MECHANISMS

Iron-catalyzed cross-coupling between organohalides or pseudohalides with Grignard reagents has been the focus of several mechanistic investigations. In this context, the identification of the various oxidation states of the active iron species involved in the catalytic cycle is of capital importance.

Due to the influence that ligands, additives and nature of the coupling partners have on the catalytic pathway, a number of catalytic cycles have been proposed. The catalytic cycle most commonly employed to describe ligand-free iron-catalyzed cross-coupling reactions resembles the well-established palladium-mediated Kumada–Tamao–Corriu cycle.[14] This catalytic cycle consists of double-electron processes, namely oxidative addition (OA) and transmetalation (TM), followed by reductive elimination (RE) as shown in Scheme 2. Whether the transmetalation or the oxidative addition occurs first is still the topic of much debate, especially since both pathways are consistent with the product outcome.



Scheme 2. Two possible pathways for the iron-catalyzed analog of the Kumada–Tamao–Corriu reaction. R = alkyl, alkenyl or aryl.

The first mechanistic model for iron-catalyzed cross-coupling was proposed in the pioneering work of Kochi in 1971. [7a] In this work, several experimental observations were made on the

coupling of alkyl halides with Grignard reagents that supported the classical Kumada–Tamao–Corriu catalytic cycle. As a prelude to the forthcoming challenges in assessing the structural details of the catalytic cycle, Kochi and co-workers alluded that an alternative catalytic pathway should be operative when alkyl halides are used as coupling partners in place of alkenyl and aryl substrates. Product distribution studies, as well as kinetic and trapping experiments revealed that, depending on the nature of the electrophile employed in the reaction, both radical and polar mechanisms could be operative and based on an Fe(I)/Fe(III) catalytic cycle.

Since the significant increase in interest in iron-catalyzed cross-coupling reactions in the early 2000s, the efforts of many research groups have focused on furthering our understanding of the mechanisms driving these iron-mediated transformations.

When iron-catalyzed cross-coupling reactions are conducted in the absence of ligands, an Fe(n)/Fe(n+2) catalytic cycle has been proposed. The lowest oxidation state of the active iron catalyst in this catalytic cycle has been the center of much debate for many years. It is thought that the oxidation state is either Fe(-II), operative in a possible Fe(-II)/Fe(0) catalytic cycle or Fe(I), which would promote an Fe(I)/Fe(III) cycle.

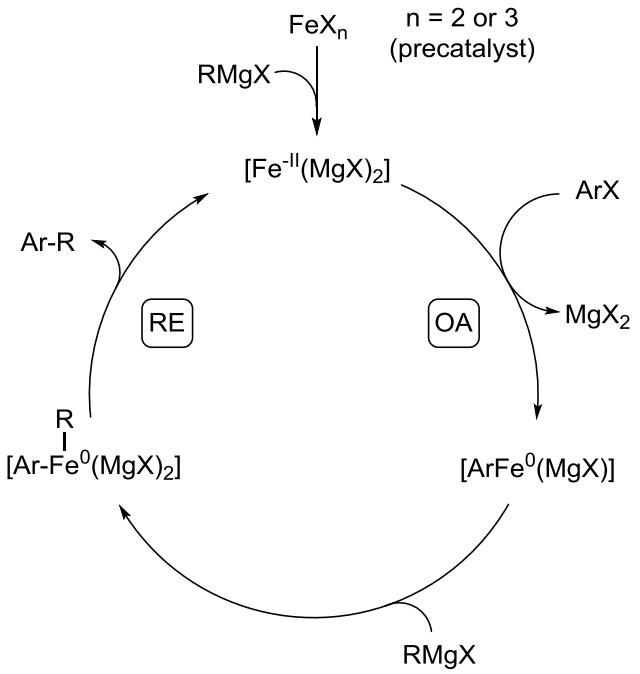
However, when ligands are present in the reaction, catalytic cycles based on both Fe(I) and Fe(II) as the lowest oxidation state have been proposed.

5. LOWEST OXIDATION STATE OF IRON IN THE Fe(n)/Fe(>n) CATALYTIC CYCLE

5.1 The Fe(-II)/Fe(0) catalytic cycle

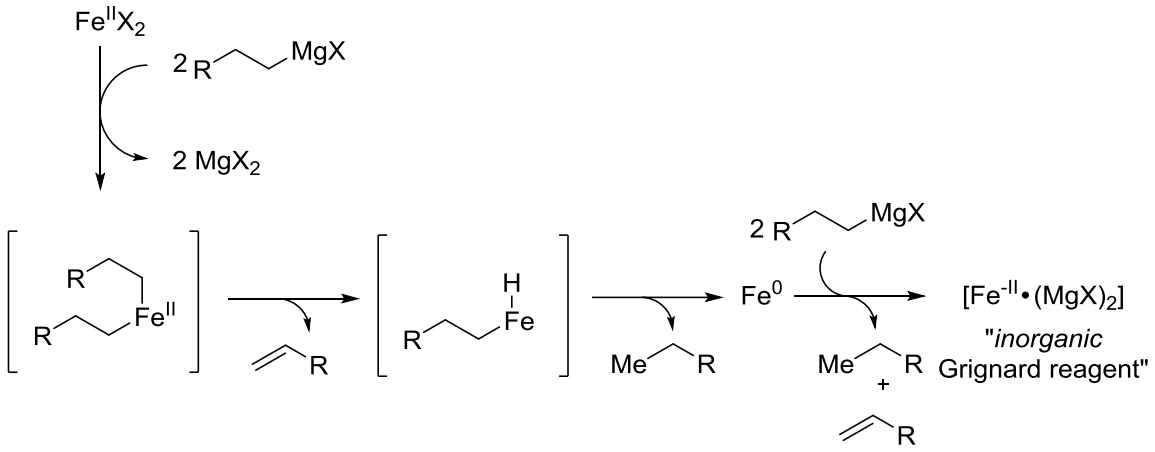
Fürstner and co-workers postulated that a catalytic cycle based on a low-valent Fe(-II) could be operative in the coupling of aryl halides with alkyl Grignard reagents.[9] Such a pathway relies on

the strong nucleophilic character of an Fe(-II) species generated *in situ*, which may be able to oxidatively insert into the aryl halide (OA). Direct alkylation of the Fe(0) intermediate with the Grignard reagent and subsequent reductive elimination (RE) results in the desired product, together with the regeneration of the Fe(-II) catalyst thus completing the catalytic cycle (Scheme 3).



Scheme 3. Proposed mechanism for the cross-coupling of aryl halides with alkyl Grignard reagents based on Fe(-II)/Fe(0) manifold. R = alkyl.

As previously reported by Bogdanović and co-workers, the initial formation of the Fe(-II) species may be derived by the *in situ* reduction of Fe(II) and Fe(III) precatalysts with Grignard reagents.[15] A low-valent species, also known as "*inorganic* Grignard reagent", was obtained from $FeCl_2$ and alkyl magnesium halide in the presence of Mg(0). The formation of this low-valent iron species was reported to occur when similar conditions to those generally used in iron-catalyzed cross-coupling reactions were employed, and was therefore suspected to play a vital role in the catalytic cycle (Scheme 4).



Scheme 4. Proposed formation of low-valent "*inorganic* Grignard reagent".

In agreement with an Fe(-II)/Fe(0) catalytic cycle, Fürstner also reported that other well-defined low-valent Fe(-II) complexes can be used as catalysts and that their catalytic activity is comparable to that of Fe(II) or Fe(III) salts.[16] Fürstner and co-workers discovered a significant difference in reactivity between MeMgBr and higher alkyl magnesium halides, supporting the role of Fe(-II) in the catalytic cross-coupling reaction between aryl halides and alkyl Grignard reagents. In particular, Grignard reagents bearing an alkyl group amenable towards β-hydride elimination resulted in high conversions of aryl chlorides to the final product. However, the reaction between MeMgBr and the same organohalides was unsuccessful toward the formation of the corresponding product.[16] This rather intriguing finding was rationalized on the basis of the pathway proposed by Bogdanović for the formation of low-valent iron complexes. Indeed, Grignard reagents that are not susceptible to β-hydride elimination should not be able to reduce the precatalyst to the catalytically active Fe(-II) species. However, such Grignard reagents would more likely promote the formation of metastable organoferrate complexes. Accordingly, these complexes, characterized by a lower nucleophilic character than the Fe(-II) species, were found to be unreactive towards poorly activated aryl chlorides. Despite their poor nucleophilicity, the

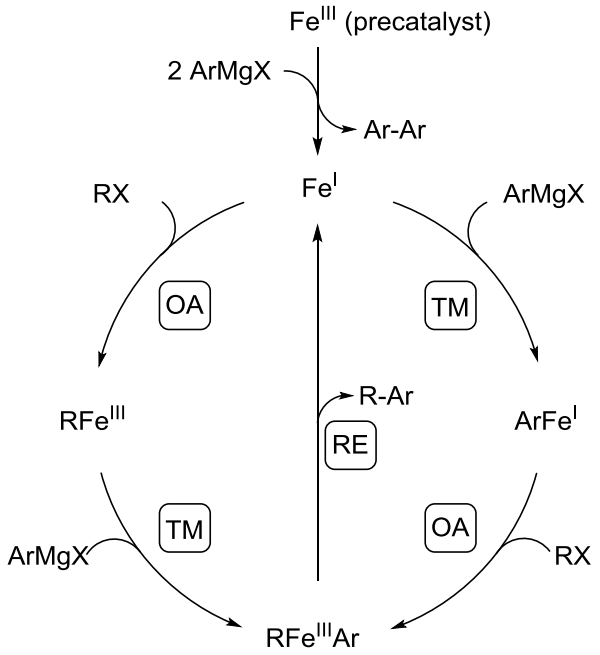
organoferrate complexes are still able to transfer their organic residue to more reactive substrates such as acid chlorides, enol triflates or electron deficient heteroarenes.

5.2 The Fe(I)/Fe(III)catalytic cycle

Even though the ability of Fe(-II) species to catalyze cross-coupling reactions of aryl halides with alkyl Grignards has been shown, an important distinction between precatalyst and active catalyst must be made as recently suggested by Bedford.[17] This author, whose work has largely defined the foundation of this mechanistic crusade, highlighted that even though the conditions reported by Bogdanović for the formation of the active Fe(-II) species are similar to the catalytic reaction conditions, in the absence of a strong reducing agent, such as Mg(0), the formation of subzero iron species should be prevented.

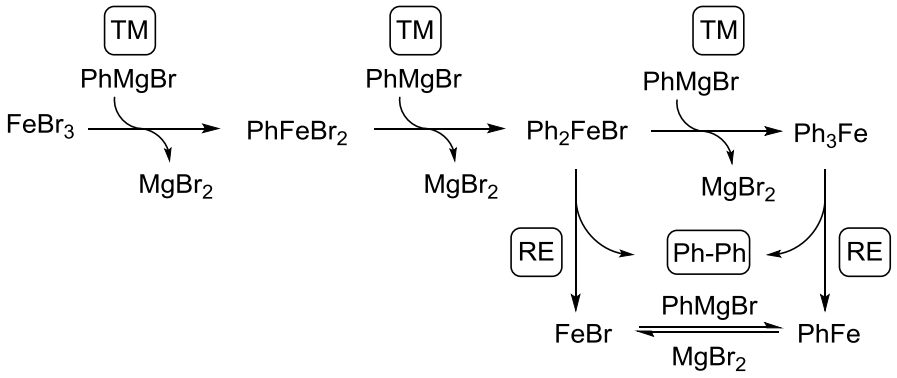
Indeed, based on kinetic and thermodynamic evaluations, the work of Norrby and co-workers ruled out Fe(-II) as the active catalyst in this type of transformations. Computational studies performed by this research group showed a prohibitive energy barrier associated with a reductive elimination pathway to subzero iron species.[18] In light of these results, low-valent iron species can be considered as efficient precatalysts, but not as active catalysts.

Moreover, a series of titration experiments, conducted in the absence of Mg(0), confirmed that the lowest oxidation state that Fe(III) salts can reach when reduced to the active catalytic species by aryl Grignards is Fe(I) (Scheme 5).



Scheme 5. Proposed Fe(I)/Fe(III) catalytic cycle for the coupling of aryl Grignard reagents and alkyl halides starting from an Fe(III) precatalyst. R = alkyl.

Under inert conditions, the titration of an Fe(III) precatalyst using small batches of aryl Grignard reagents led to the fast formation of biphenyl and a reduced iron species, showing a reproducible stoichiometry close to 1. Since the formation of biphenyl from Grignard reagents is a two electrons process, the results represent a strong indication that iron is reduced to Fe(I). Even in the presence of excess Grignard reagent, further reduction of this iron species is not observed.[19] Computational investigations using dispersion-corrected DFT methods, indicated that two consecutive exergonic transmetalations take place to generate a diarylated Fe(III) species. This is then followed by reductive elimination, affording the homo-coupling product and the generation of the Fe(I) species (Scheme 6). The same set of calculations also suggested a pathway involving a triarylated Fe(III) complex, generated *via* three consecutive transmetalations. However, this was found to be less probable.



Scheme 6. Proposed homo-coupling reaction mechanism and formation of the active catalyst.

Contrary, Neidig and co-workers recently identified and characterized an important tetralkyliron(III) ferrate complex, which was also found to be an intermediate in the reduction of $FeCl_3$ by alkyl Grignard. Importantly, this intermediate spontaneously converts to an EPR-active iron species (S = 1/2), which is believed to be the active catalyst.[20] When alkyl Grignards were used in analogous conditions in the place of aryl Grignard reagents, different iron species have been observed. In the alkyl-aryl cross-coupling reaction, an excess of highly reducing alkyl magnesium halide results in catalyst deactivation.[21] This observation was found to be consistent with a dual catalyst activity, where the excess Grignard converts the active catalytic species into a less active form. It is speculated that this catalyst deactivation pathway is responsible for solution darkening and salts formation in the cross-coupling reaction between aryl halides and excess of alkyl Grignard reagent. Additionally, it provides an explanation for the increase performance of the reaction when the Grignard reagent is added slowly to the reaction mixture.

Moreover, a reaction order close to 1 has been observed for the Grignard nucleophile at concertation typically employed in iron-catalyzed cross-coupling reactions.[18,46] This strongly suggests that transmetalation occurs before the oxidative addition, which is the rate-determining step.

Furthermore, Bauer and Werner supported Fe(I) as the lowest oxidation state in such reactions by using X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS) techniques.[22]

5.2.1 The Fe(I)/Fe(III) catalytic cycle in the presence of ligands

Many efforts have been devoted to further our understanding of the mechanistic pathway of iron-catalyzed cross-coupling reactions between organohalides and various nucleophiles in the presence of a variety of ligands.

The majority of reports in the literature suggests that an Fe(II)/Fe(III) catalytic cycle occurs when ligands are involved (*vide infra*). However, observations mainly made by the groups of Bedford, Cárdenas and Neidig suggest that, in the presence of specific ligands, iron can reach oxidation state of 1 or lower in the iron-catalyzed variation of the Kumada–Tamao–Corriu reaction. [23,24,25,26]

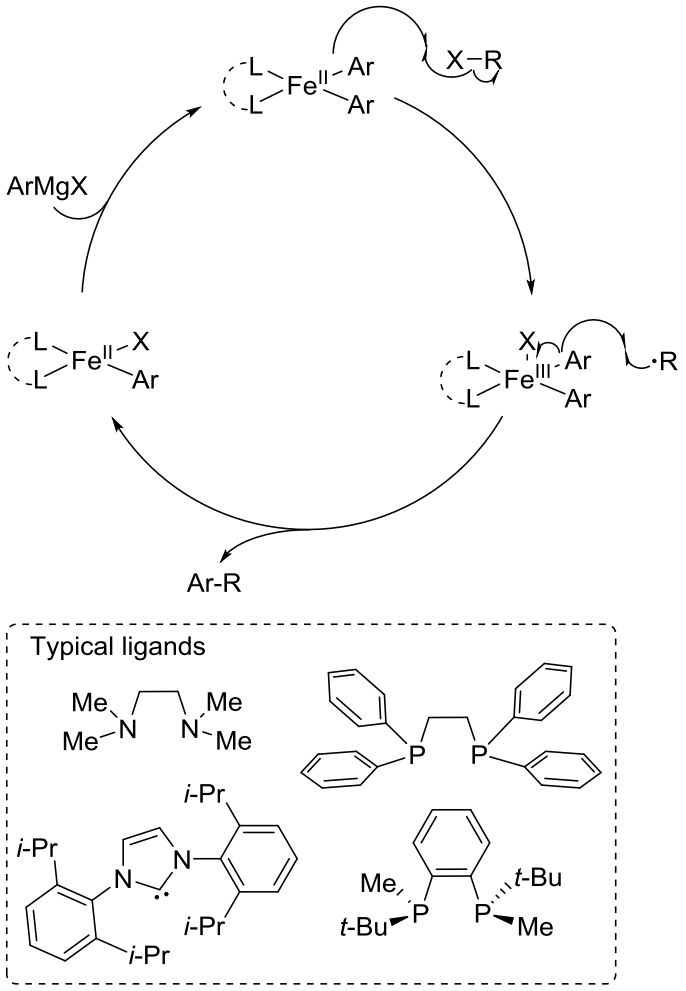
EPR analysis performed by these groups showed that, in the presence of biphosphines or NHC type ligands, a low-spin iron species ($S = 1/2$) is observed. In line with this observation, several studies have been performed on the reactivity of isolated Fe(I) complexes with biphosphine ligands.[27,28] In particular, Bedford and co-workers reported the X-ray characterization of several Fe(I) catalysts and intermediates. DFT calculation performed on these complexes showed that the Mulliken spin density corresponding to the unpaired electron is mainly centered on the iron atom. [23,29] The same group also suggested that the nature of the Fe(I) species depends on how bulky the chelating biphosphines employed are. For very bulky biphosphines, mono-chelated Fe(I) complexes are more likely produced over bis-chelated Fe(I). The group of Neidig also reported the presence of low-spin iron species ($S = 1/2$) when a very bulky biphosphine ligand

(SciOPP) was employed in combination with PhMgBr. However, spin quantitated EPR indicated that only <0.5% of a possible low spin Fe(I) was formed in the reaction.[26]

All these reports provide support for the formation of Fe(I)-ligand complexes under catalytically relevant conditions. It is still not clear, though, whether they are off-cycle, on-cycle or in equilibrium with the active catalytic species.

5.3 The Fe(II)/Fe(III) catalytic cycle

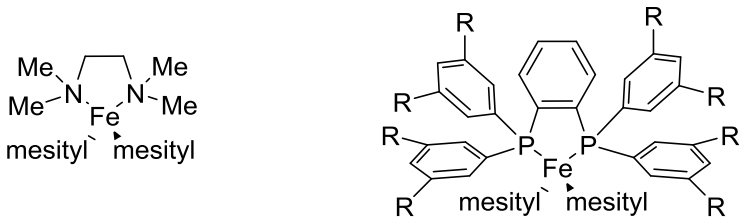
In the presence of ligands (such as bisamines, NHC and biphosphines), Fe(II) has more frequently been described as the active catalytic species in the iron-catalyzed cross-coupling reaction between alkyl halides and Grignard reagents. Under these conditions, an Fe(II)/Fe(III) catalytic cycle has been proposed based on the evidence mainly presented by the groups of Neidig, Nagashima, Nakamura and Tonzetich (Scheme 7).[12c,25,30,31,32] As often proposed for iron-catalyzed radical polymerizations,[33] the alkyl radical may be generated by an halogen-abstraction from the organohalide to the Fe(II) complex.



Scheme 7. Proposed Fe(II)/Fe(III) catalytic cycle for the cross-coupling of aryl magnesium halides and alkyl halides.

In contrast to the previously described ligand-free transformations, it is thought that, due to the steric and electronic effects that the ligands have on the reductive elimination step, the lowest oxidation state of all relevant catalytically active iron complexes in the cross-coupling reaction is an Fe(II) species. Indeed the use of sterically demanding mesityl Grignard reagents in combination with TMEDA or SciOPP ligands allowed for the formation of stable Fe(II) complexes not amenable to reductive elimination (Figure 1). These intermediates were isolated and characterized, and their reactivity furnished a valuable source of data for several mechanistic

investigations.[30,31] However, it is important to notice that the use of sterically encumbered nucleophiles, may not represent a general model for iron catalyzed cross-couplings.



$FeMes_2(TMEDA)$

$FeMes_2(SciOPP)$

Figure 1. TMEDA and SciOPP containing mesityl Fe(II) complexes.

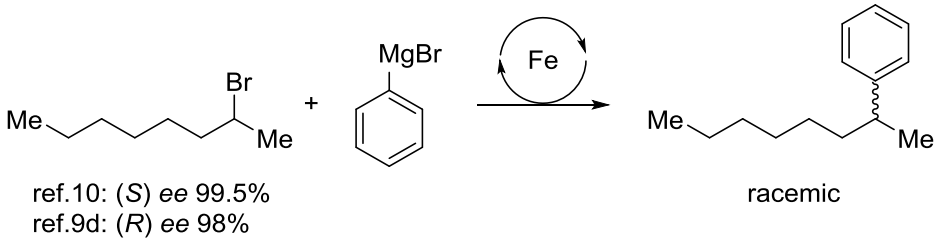
Work lead by Neidig has significantly advanced our understanding on the underlying mechanism of iron-biphosphine catalyzed variation of Kumada–Tamao–Corriu and Suzuki–Miyaura reactions. [25,26] The use of spectroscopic methods (Mössbauer, MCD, EPR) and detailed reaction studies allowed for the identification and quantification of the iron species, formed *in situ*, in the cross-coupling of aryl nucleophiles and secondary alkyl halides. An Fe(II)/Fe(III) cycle is thought to be responsible for cross-coupling reactions with both phenyl and mesityl nucleophiles. However, when phenyl nucleophiles were used in the reaction, Fe(0) species generated *via* reductive elimination of biphenyl have been observed and proposed as an off-cycle species. Radical clocks and racemization of enantioenriched electrophiles have also been provided to corroborate the proposed catalytic cycle based on single-electron processes (*vide infra*).

6. EVIDENCE FOR SINGLE-ELECTRON PROCESSES

6.1 On the radical nature of the Fe(II)/Fe(III) catalytic cycle

For iron-catalyzed cross-coupling reactions between alkyl halides and aryl nucleophiles in the presence of appropriate ligands, that are thought to proceed *via* an Fe(II)/Fe(III) catalytic cycle, a number of studies reported the formation of alkyl radical intermediates.

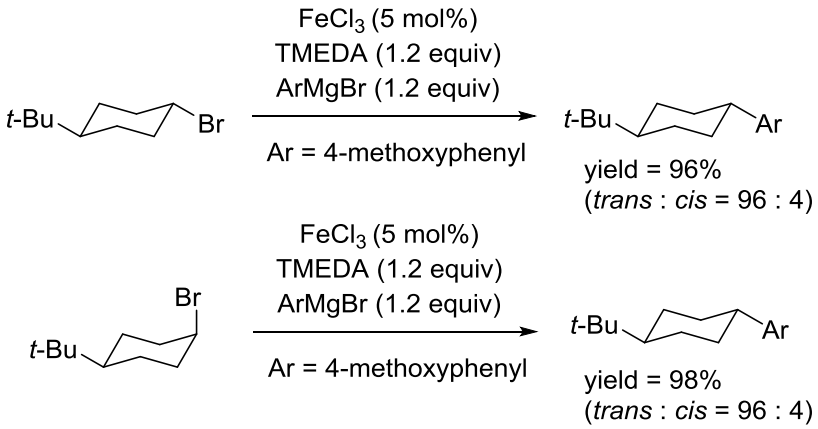
For example, the groups of Fürstner and Nakamura observed the racemization of enantioenriched secondary alkyl bromides when reacted with PhMgBr under iron-catalyzed conditions (Scheme 8).[9d,10]



Scheme 8. Racemization of enantioenriched secondary alkyl bromides in the iron-catalyzed cross-coupling with phenyl Grignard reagents.

Nakamura and co-workers have also observed the racemization of enantioenriched alkyl chlorides when treated with PhMgBr under Fe/NHC catalysis (example not shown).[34]

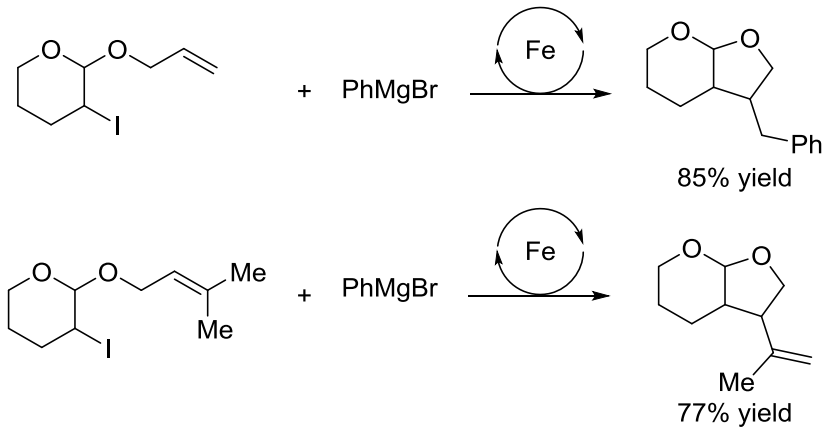
Furthermore, Nakamura has shown that the cross-coupling reaction of *trans*- and *cis*-1-bromo-4-*tert*-butylcyclohexane with aryl Grignard reagents only gives the corresponding *trans*-coupling product *via* a diastereoconvergent pathway (Scheme 9).[10]



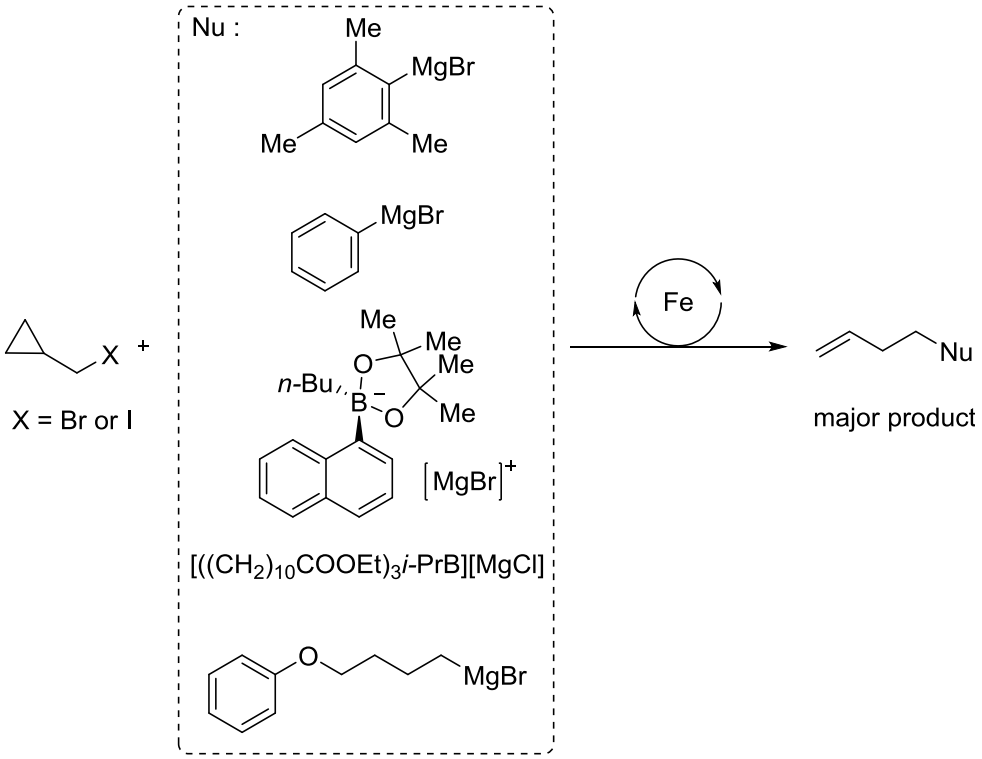
Scheme 9. Diastereoconvergent cross-coupling of *trans*- and *cis*-1-bromo-4-*tert*-butylcyclohexane with aryl Grignard reagents.

Since a catalytic cycle based on a double-electron oxidative addition would be more likely stereospecific, a radical pathway was proposed to explain the loss of chiral and geometrical information of the starting material.

Moreover, Fürstner and co-workers reported that the ring-closure of 2-(allyloxy)-3-iodotetrahydro-*2H*-pyran derivatives occurs prior to cross-coupling with aryl Grignard reagents (Scheme 10).[9d] Even though these results may be in agreement with the presence of radical intermediates, the reactions were substrate dependent and other pathways proceeding without the formation of radical intermediates (e.g. Heck-type cross-coupling) cannot be excluded.



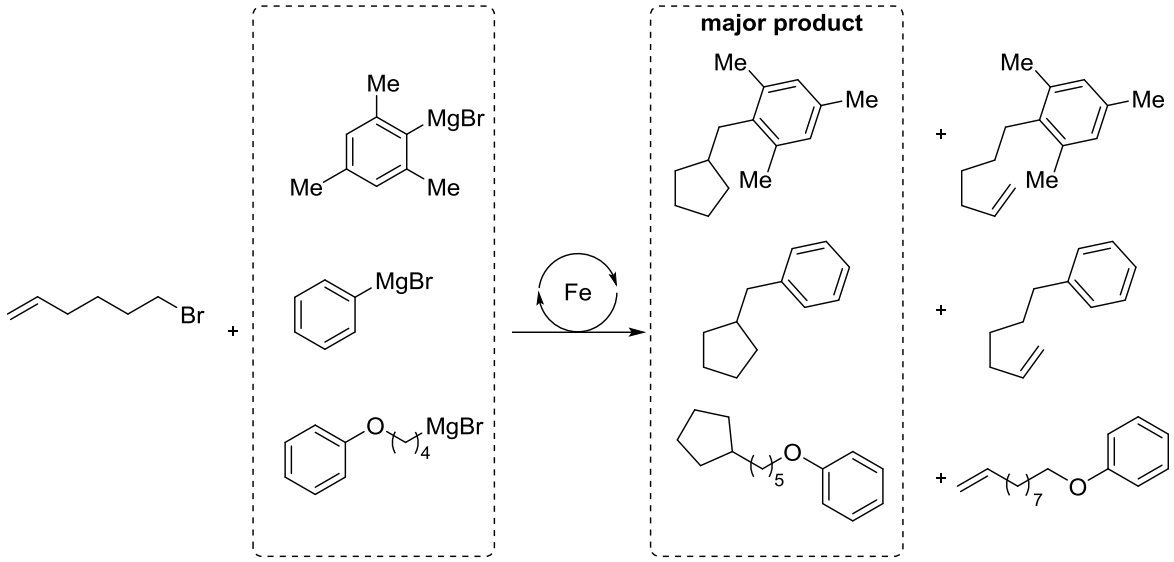
Scheme 10. Ring-closure of 2-halo acetal derivatives under iron-catalyzed conditions.



Scheme 11. Use of radical clock as electrophile in the cross-coupling reaction.

Halomethylcyclopropane (radical clock) is commonly used as a mechanistic probe to support radical mediated cross-coupling reaction (Scheme 11). As reported by Bedford, Nakamura, Nagashima, Cossy and Chai, when such a mechanistic probe was used in combination with various nucleophiles, the reactions depicted in Scheme 11 proceeded with almost complete selectivity toward the ring-opened product. [12c,12b,24,30,31,35,36,37,38]

Similarly, the iron-catalyzed reaction of 6-bromo-1-hexene with Grignard reagents has been used to support a possible radical pathway. This transformation, reported with aryl Grignards by Nagashima and Bedford,[12c,30] and with alkyl Grignards by Chai,[38] formed the corresponding cyclopentane derivatives as the major product (Scheme 12).



Scheme 12. Iron-catalyzed reaction of 6-bromo-1-hexene with Grignard reagents.

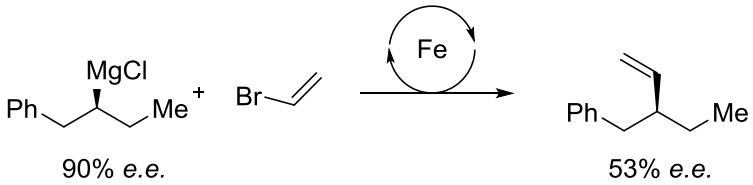
Although these last two examples, that are based on radical clocks and intramolecular cyclization, corroborate well with the formation of an alkyl radical intermediate, the outcome of these studies can alternatively be explained by invoking a metal-catalyzed cyclopropane ring opening and a Heck-type addition, respectively (Scheme 11 and 12). Consequently, any mechanistic proposal based only on the chemical outcome observed in the reactions reported in Scheme 10, 11 and 12 are supportive of a radical mechanism, but not conclusive.

In addition, looking for evidence towards radical generation in these types of transformations, the challenges associated with the application of iron catalysts to asymmetric organometallic transformation should be a matter of consideration.[39] Only very recently, Nakamura disclosed the first enantioselective cross-coupling between alkyl chlorides and aryl Grignard reagents.[40] Also, in this remarkable piece of work, a radical mechanism involving the generation of an alkyl radical intermediate has been further supported by radical probes.

6.2 On the radical nature of the Fe(I)/Fe(III) catalytic cycle

Regarding the nature of iron-catalyzed cross-couplings under ligand-free conditions, many evidence points towards a radical mechanism being operative when sp^3-hybridized electrophiles

are used in combination with Grignard reagents.[41] Concerning sp^2-hybridized electrophiles, to our knowledge, the sole evidence based on a racemization experiment in support for a radical pathway was provided by Hoffmann, who showed partial racemization of enantioenriched secondary Grignard reagents in the iron-catalyzed coupling with vinyl bromide (Scheme 13).[42]



Scheme 13. Partial racemization of enantioenriched secondary Grignard reagents in the iron-catalyzed coupling with vinyl bromide.

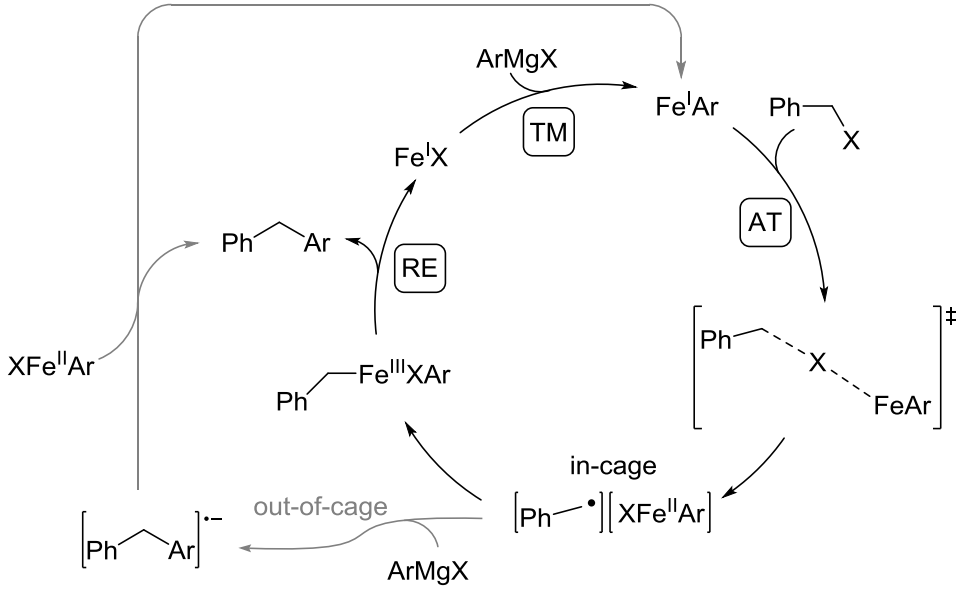
In the absence of additional evidence supporting a radical mechanism involving such electrophiles, the most commonly invoked reaction pathway is based on double-electron processes operative in an Fe(I)/Fe(III) catalytic cycle.[18,19,21,22,43]

The generation of radical intermediates when using sp^3-hybridized electrophiles was first proposed by Kochi in 1971.[7a] In this report, a trapping experiment utilizing styrene as radical scavenger, showed a selective trapping when alkyl halides were employed in the cross-coupling reaction. Chemically Induced Dynamic Nuclear Polarization (CIDNP) experiments further supported the generation of free radicals from the alkyl halide reaction component.[44]

Moreover, Oshima reported the ring-closure of 2-haloethanal allyl acetals in the presence of iron salts and PhMgBr, which is also in agreement with the formation of alkyl radicals.[45]

Further support for the radical nature of oxidative addition in iron-catalyzed cross-coupling reactions between Grignard reagents and saturated organohalides, comes from kinetic investigations recently performed by Norrby co-workers.[46] An initial competitive Hammett study was performed to account for the electronic effects imposed by the arylmagnesium bromide in the coupling with cyclohexylbromide. The negative ρ-value observed was consistent with the

oxidative addition being both the rate-limiting and the selectivity-determining step. To probe the potential radical nature of the transformation, a new Hammett study was devised using a set of substituted benzylic halides as the electronically differentiable variable. The correlation coefficients were found to be close to 1, indicating a constant reaction order throughout the reaction. For this reason, an off-cycle deactivation pathway, similar to the one proposed for aryl halides, was excluded under these conditions. More importantly, the obtained data clearly showed that all variation of the *para*-substituent accelerate the reaction rate relative to the unsubstituted benzyl halide.



Scheme 14. Proposed mechanism for an atom-transfer mediated cross-coupling reaction.

The results suggest a radical mechanism in which a benzylic radical intermediate, more likely generated *via* an atom-transfer rather than a single-electron transfer, is involved in the transformation (Scheme 14). This stands against a classical three-centered concerted mechanism as proposed for sp^2-hybridized organohalides. Following the atom-transfer event, responsible for the generation of the benzylic radical and the Fe(II) complex, an in-cage recombination of these two species provides the product through reductive elimination. Alternatively, the benzylic

radical may escape from the solvent cage and combine with the aryl Grignard reagent to provide the corresponding radical anion (out-of-cage path, Scheme 14). This entity can then transfer an electron to the Fe(II) species to afford the product together with Fe(I). Independently from the fate of the radical, Hammet and DFT studies also implied an early transition state with a strong radical character.

7. CONCLUSIONS

Nowadays, there is a fair consensus that the catalytic cycle for iron-catalyzed cross-couplings of organohalides with Grignard reagents include Fe(III) as the highest oxidation state. In the presence of ligands, experimental evidence supporting both Fe(I)/Fe(III) and Fe(II)/Fe(III) catalytic cycles has been reported. While the debate on the lowest oxidation state of the iron active catalyst is still open, there is convincing evidence that the process proceeds *via* a radical pathway.

Under ligand-free conditions, it has been shown that iron can reach the Fe(I) oxidation state, allowing an Fe(I)/Fe(III) catalytic cycle. For alkyl halide electrophiles, there are strong indications that the reaction proceeds through single-electron steps. An atom-transfer event is likely to be responsible for the formation of the alkyl radical together with an Fe(II) species. It is still not clear as to whether the radical combines with the Fe(II) species to give Fe(III), which than rapidly undergoes reductive elimination, or whether the radical directly reacts with a Grignard reagent to form a radical anion that can transfer an electron to an iron complex to give the final product.

For the reaction of alkyl Grignards with sp^2-hybridized organohalides under ligand-free conditions, the presence of radical intermediates remains unclear and a mechanism based on double-electron processes is more widely accepted. Hammett studies have excluded the

possibility of SET to aryl halides, but an atom-transfer pathway may still be plausible. The C(sp^2)-halide bond is stronger than the corresponding C(sp^3)-halide bond, which would reduce the likelihood for atom-transfer processes. Intermediate radicals could potentially be trapped with substrates, such as 2-iodo-allyl benzene, or be detected by CIDNP experiments, but to the best of our knowledge, conclusive evidence has not yet been obtained. Despite this, it is clear that the presence of strongly reducing alkyl Grignard reagents in high concentration, can facilitate off-cycle deactivating pathways.

We believe that the remarkable achievements obtained thus far in the mechanistic investigation of iron-catalyzed C–C bond forming cross-coupling reactions represent a solid foundation for future mechanistic exploration and consequent expansion of the frontiers of this valuable synthetic approach.

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Notes

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ABBREVIATIONS

NHC, *N*-heterocyclic carbene; DFT, Density Functional Theory; MCD, magnetic circular dichroism; EPR, electron paramagnetic resonance; SET, single-electron transfer; TMEDA, tetramethylethylenediamine; AT, atom-transfer; OA, oxidative addition; RE, reductive elimination; TM, transmetalation.

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