Coming of Age: Sustainable Iron-Catalyzed Cross-Coupling Reactions


Dedicated to Jay K. Kochi

Artwork by von Wangelin design (Rostock, Germany)
Iron-catalyzed carbon–carbon bond-forming reactions have matured to an indispensable class of reactions in organic synthesis. The advent of economically and ecologically attractive iron catalysts in the past years has stepped up the competition with the established palladium and nickel catalyst systems that have dominated the field for more than 30 years, but suffer from high costs, toxicity, and sometimes low reactivity. Iron-catalyzed protocols do not merely benefit from economic advantages but entertain a rich manifold of reactivity patterns and tolerate various functional groups. The past years have witnessed a rapid development with ever-more-efficient protocols for the cross-coupling between alkyl, alkenyl, alkynyl, aryl, and acyl moieties becoming available to organic chemists. This Review intends to shed light onto the versatility that iron-catalyzed cross-coupling reactions offer, summarize major achievements, and clear the way for further use of such superior methodologies in the synthesis of fine chemicals, bioactive molecules, and materials.

Introduction

Over the past decades, transition-metal-catalyzed cross-coupling reactions have gained a strong foothold within the arsenal of powerful carbon–carbon and carbon–heteroatom bond forming reactions. Palladium, nickel, and copper catalysts have so far taken center stage when it comes to the synthesis of complex and functionalized organic molecules involving cross-coupling reactions. Numerous applications document their advantageous use with respect to generality and functional-group tolerance. However, the stressing of modern efficiency criteria has prompted the search for alternative catalysts that address the economic and ecological disadvantages associated with the use of palladium and nickel catalysts. With an average price of $300 per ounce, palladium is the bull of any synthesis it is employed in, especially in the context of manufacturing on larger scales. Various toxicity aspects taint the use of nickel-catalyzed processes for consumer goods and healthcare products. Furthermore, both palladium and nickel catalyst systems usually require the addition of structurally complex and costly ligands of high molecular weight.

Iron catalysts have recently been introduced to address these economic and ecological challenges. A multitude of biological systems and functions rely upon the rich chemistry of iron-containing enzymes. Iron is an essential metal for the life cycle of all living things, and thus constitutes an attractive metal for man-made synthetic transformations as no severe toxicity and side effects exist. Albeit the first iron-catalyzed homo-coupling of aryl Grignard reagents was described by Kharasch and Fields already in 1941, the genuine era of iron-catalyzed cross-coupling reactions originated in the early 1970s, predating its palladium and nickel relatives, when Kochi carefully studied reactions of alkenyl halides with Grignard reagents. Although limited with respect to catalytic activity and substrate scope, the first mechanistic rationale for such iron-catalyzed cross-coupling was put forward. It invoked an analogy to the Pd and Ni systems, where a coordinatively unsaturated reduced iron complex (of unspecified constitution) sequentially undergoes oxidative addition of the organohalide, transmetallation from the organomagnesium species, and reductive elimination of the cross-coupling product. Some isolated publications perpetuated the interest in this class of reactions through the 1990s, but it was not until the early 2000s that the development of iron-catalyzed cross-coupling reactions really picked up momentum. Fürstner and Leitner then reported on an optimized protocol for the highly selective iron-catalyzed reaction of aryl halides with alkyl magnesiumhalides in the presence of NMP as co-solvent. This work was the go-ahead signal for a series of forthcoming publications contributing to the development of ever-more-efficient and widely applicable protocols. Based upon the pioneering work by Kochi and spurred on by recent developments, iron-catalyzed cross-coupling reactions have since matured to a multifaceted class of effective C–C and C–X bond-forming reactions with a wide substrate scope and functional group tolerance.

This Review summarizes the most significant milestones in the quest for efficient carbon–carbon bond-forming cross-coupling reactions under iron catalysis, and highlights synthetically useful protocols that constitute a serious competition for the established palladium and nickel catalyst systems. It is the clear intention of this Review to familiarize the reader with the history and state-of-the-art of iron-catalyzed carbon–carbon bond forming cross-coupling reactions. In order to reach a wide perspective, all scientific contributions revolving around iron-catalyzed cross-coupling between an organic electrophile bearing a leaving group and an organometallic (or hydrocarbon) nucleophile (i.e., a formal substitution reaction) are covered up to March 2009 (Scheme 1). The Heck reaction would not fall into such a definition, but as it involves a formal substi-
Cross-Coupling with Alkenyl Electrophiles

The potential of iron catalysis for cross-coupling reactions was first tapped by the seminal work of Kochi and his group as early as 1971. The studies revealed that alken-1-yl halides, in marked contrast to alkyl halides, readily reacted with Grignard reagents in the presence of catalytic amounts of FeCl₃ to give cross-coupling products with high stereoselectivity (Scheme 2).[7] At ambient temperature and 0 °C, good yields of the coupled product (up to 83 %) were obtained within a few hours, although a large excess of the vinyl halide was required. The extension of this work allowed for the use of secondary and tertiary alkyl and aryl Grignard reagents.[11] Various iron complexes and the effect of their aging on the catalytic activity were evaluated by UV spectroscopy and conversion experiments. High rates of cross-coupling reactions were limited by deactivation of the catalyst owing to an aging process attributed to the aggregation of the active iron species (Figure 1). It was proposed that the active low-valent catalyst is generated through the reduction of iron salts with alkyl Grignard reagents.[12]

In Kochi’s studies, Fe(acac)₃ and Fe(dbm)₃ both proved equally active. The stereogenic information of 1-bromopropane was preserved during the transformation. Based on kinetic studies and electron paramagnetic resonance, a mechanism of the iron-catalyzed cross-coupling of vinyl bromides with Grignard reagents was proposed as depicted in Scheme 3.[13] In 1978, Felkin and Meunier published a stereoselective cross-coupling reaction between alkenyl bromides and phenyl Grignard reagents with iron–phosphine catalysts.[14] The cross-coupling product is formed in high yield and stereoselectivity.
alkenyl halides with aryl Grignard reagents to provide aryl ethenes. It was found that DME as solvent consistently provided the highest yields of the desired cross-coupling product. Furthermore, no excess of alkenyl halide was required, and a lower initial reaction temperature (−20 °C) proved beneficial (Scheme 5).[17]

\[
\text{Ph} \quad \text{H} \quad \text{Br} \quad + \quad \text{ArMgX} \quad \text{1 mol% Fe(acac)}_3 \quad \text{DME, -20 to 20 °C, 2 h}
\]

\[
\begin{align*}
\text{Ar:} & \quad \text{phenyl} \quad 68\% \\
& \quad 3\text{-methoxyphenyl} \quad 75\% \\
& \quad 1\text{-naphthyl} \quad 56\% \\
& \quad 4\text{-chlorophenyl} \quad 75\% \\
& \quad \text{o-tolyl} \quad 100\% \\
& \quad 2,4,6\text{-trimethylphenyl} \quad 0\% 
\end{align*}
\]

Scheme 5. Fe(acac)$_3$-catalyzed coupling of vinyl bromides with aryl Grignard reagents by Molander et al.[17]

Naso and coworkers showed that various iron compounds such as Fe(dbm)$_3$, Fe(dpm)$_3$, Fe(acac)$_3$, and FeCl$_3$ catalyze the cross-coupling of (E)- or (Z)-1-bromo-2-phenylthioethenes with aryl Grignard reagents in THF at −78 °C affording alkenyl sulfides in good yields with high chemo- and stereoselectivity.[18] The cross-coupling reaction between stoichiometric amounts of alkyl–Fe$_2$ species (such as MeFeCl·2 LiCl, Me$_2$Fe·3 LiCl, and Me$_3$FeLi·3 LiCl) and vinyllic bromides or acyl chlorides was described by Kauffmann et al.[19] The iron reagents also proved reactive towards aldehydes and ketones bearing a chelating group. Cahiez and coworkers developed a general procedure for the iron-catalyzed alkenylation of organomanganese compounds using mixtures of THF and NMP. As the reactivity was greatly enhanced in this solvent system, the amount of the organomanganese reagent could be significantly reduced (Scheme 6).[20]

Scheme 6. Alkenylation of Grignard reagents by Cahiez et al.[20a]

The same authors later reported on a highly stereoselective iron-catalyzed alkenylation of organomagnesium compounds. The chemoselectivity was demonstrated by the tolerance towards various functional groups (esters, nitriles, halides, and even ketones). A screening of various cosolvents in model reactions of alkenyl halides (X=I, Br, or Cl) with Grignard reagents revealed that the use of NMP resulted in shorter reaction times, higher yields, and excellent stereoselectivity. The authors assumed that one of the roles of NMP might be the minimization of decomposition processes (i.e., β-hydride elimination) by stabilizing intermediate iron species. The loading of the catalyst could be lowered to 0.01 mol% in selected cases. This methodology was also applied to enol phosphates (Scheme 7).[21] The potential of organomanganese reagents for such reactions proved even more profound as Fürstner and
Brunner reported on a novel generation of various alkyl, alkenyl, aryl, and heteroaryl manganese reagents directly from alkyl halides and activated manganese. Highly active Mn–graphite was formed upon reduction of MnBr₂·nLiBr (n = 1, 2) with K–graphite (Scheme 8).[22]

Collaborative work by Cahiez and Knochel focused on the exploitation of functionalized arylmagnesium reagents bearing ester, cyano, nonaflate, or trialkylsilyloxy groups generated by halogen–metal exchange with iPrMgBr. Rapid reactions with alkenyl iodides or bromides in the presence of catalytic amounts of Fe₃C₂H₅₆ (5 mol %) at /C₀₂⁰°C resulted in the formation of the desired cross-coupling products as exclusively E isomers with satisfactory yields (Scheme 9). Good results could also be achieved by performing the cross-coupling reaction on a solid phase by generating the Grignard reagent on Wang resin.[23]

The NMP protocol of Cahiez was later applied by Begtrup and coworkers in the synthesis of 3-substituted N-Boc-protected pyrrolidines. Primary and secondary alkylmagnesium halides were reacted in THF/NMP at /C₀°C. Aryl Grignard reagents proved to be less reactive; tertiary Grignards did not react (Scheme 10).[24]

Hölzer and Hoffmann reacted a chiral Grignard reagent, in which the magnesium-bearing carbon atom was the sole stereogenic center, with vinyl bromide under catalysis of various transition metals.[25] Whilst Pd⁰- and Ni⁰-catalyzed reactions proceeded with full retention of configuration, considerable racemization occurred in the presence of Fe₃C₂H₅₆ and Co₃C₂H₅₆ as catalysts (Scheme 11). This outcome established the transmetallation of the Grignard reagent to Pd II or Ni II as a concerted S E₂-ret process, while in the case of iron and cobalt, a single electron transfer (SET) might be operative.

The group of Itami and Yoshida described an iron-catalyzed cross-coupling reaction of alkenyl sulfides with Grignard reagents. While the cross-coupling proceeds efficiently at alkenyl/C₀S bonds, almost no reaction takes place at aryl/C₀S bonds, suggesting a unique selectivity of iron catalysts (Scheme 12).[26] The authors surmise that an addition–elimination mechanism might be involved.

Furstner and coworkers devised a protocol for the coupling reaction of a variety of alkenyl triflates derived from ketones, β-keto esters, or cyclic 1,3-diketones with functionalized organomagnesium halides bearing ether, acetal, alkyne, or trime-
thylsilyl groups or aryl chloride entities in their backbones (Scheme 13). This procedure was also applied by Fürstner et al. in syntheses of Latrunculin B, (-)-α-cubene, and (-)-α-Cubebol.

A modified protocol was used by Camacho-Dávila in the synthesis of Combretastatin A-4 (Scheme 14). Further applications of the Fe(acac)₃/THF/NMP protocol to coupling reactions of enol triflates were realized in the synthesis of biologically active compounds such as Ciguatoxin segments, Agarospirin, α-Vetispirene, and Cedrene and Cedrol.

On the other hand, highly reduced metal clusters such as [Fe(MgX)₂]ₙ might be the active species when EtMgX or higher alkyl Grignard reagents are employed. Their behavior can be mimicked by structurally well-defined lithium ferrate complexes bearing only kinetically labile olefin ligands. Such electron-rich and highly nucleophilic complexes cleanly react with prototype substrates amenable to catalytic cross-coupling. It was demonstrated that formal oxidation states of iron ranging from -2 to +3 are to be considered in cross-coupling reactions and that different intertwined catalytic cycles might be populated. In line with this notion, it is possible to prepare the ate-complex [Me₄Fe][Li₂(OEt)₂] as a thermolabile and highly air-sensitive compound by reaction of MeLi with FeCl₃. Treatment of triflates with this defined reagent afforded the coupling products in similar yields as obtained under “in situ” conditions (Scheme 17).

Fürstner et al. showed that strained cyclobutanyl iodides prepared by ruthenium-catalyzed enyne cycloisomerization are catalyzed by a modified protocol used by Camacho-Dávila in the synthesis of Combretastatin A-4 (Scheme 14). Further applications of the Fe(acac)₃/THF/NMP protocol to coupling reactions of enol triflates were realized in the synthesis of biologically active compounds such as Ciguatoxin segments, Agarospirin, α-Vetispirene, and Cedrene and Cedrol.
susceptible to further functionalization with Grignard reagents under iron catalysis. The groups of Alami and Figadère jointly investigated the iron-catalyzed cross-coupling reaction between 1,1-dichloro-1-alkenes and Grignard reagents. This reaction led mainly to double substitution in good to excellent yields and required mild conditions (–30 °C, THF). However, when 3 equivalents of c-hexylmagnesium bromide were used, the reaction stopped at the monoalkylation stage (Scheme 18).

Interestingly, analogous 2-aryl-1,1-dibromo-1-alkenes gave the hydrodebrominated products under almost identical reaction conditions (THF/NMP). Hayashi and Berthon-Gelloz used the Fe(acac)₃-catalyzed coupling of enol triflates with Grignard reagents in the synthesis of C₂-symmetric bicyclo[2.2.1]hepta-2,5-dienes (Scheme 19). In comparison to the palladium- or nickel-catalyzed alternatives, iron was found to be superior in terms of efficacy and selectivity.

In 2008 Cahiez et al. described an efficient stereoselective coupling of enol phosphates with alkyl Grignard reagents. Coupling of dienol phosphates led to terminal conjugated dienes. The synthetic utility is illustrated by the synthesis of Diparopsis castanea (Scheme 22). A related iron-mediated methylation protocol (5 eqs. Fe(acac)₃) was recently exploited by Hayashi and Nakada for the stereoselective construction of a trisubstituted (Z)-alkene side chain of MK8383, an inhibitor of microtubulin assembly.

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(Scheme 23). Functionalities such as aryl chloride, ester, or Weinreb amide were unaffected. However, when the iron catalyst was omitted, the reaction proceeded cleanly at the Weinreb amide site. The mild reaction conditions make this protocol an efficient alternative for the synthesis of imines compared to the forced conditions normally used in condensation reactions.

Unlike acylating cross-coupling reactions with acyl chlorides, sulfinyl chlorides are subject to SO₂ extrusion. Rao Volla and Vogel disclosed reaction conditions for the desulfinylative C–C cross-coupling of alkenyl sulfonyl chlorides with aryl Grignard reagents to give substituted arenes with up to 82% yield.

Chloroenynes efficiently react with Grignard reagents under iron(III) catalysis as reported in a publication by the groups of Alami and Figadère. Various functionalized unsaturated vinyl chlorides were rapidly coupled at 0 °C in THF/NMP without any interference with several functional groups, for example, propargyl acetate, ethyl benzoate, aryl bromide or hydroxyl group (Scheme 24).

Marchese and coworkers showed that the use of catalytic Fe(acac)₃ renders efficient acylations at ambient temperature. The conditions tolerated ester and nitrile functions and two different alkyl chains were successfully introduced onto carbonochlorido-thioates (Scheme 27). This procedure was applied by Ritter and Hanack in the facile synthesis of cycloheptatrienylketones.

Cahiez et al. demonstrated that iron-catalyzed acylation of organomanganese reagents can be efficiently employed for the preparation of 2- and 3-acylfurans in high yields and exploited such intermediates for the synthesis of Elsholtzione, Naginata ketone, and Perilla ketone (Scheme 28).

Cross-Coupling with Acyl Electrophiles

Reaction of Grignard reagents and other organometallic species with acyl chlorides usually proceeds in the absence of any transition-metal catalyst, but high reaction temperatures and formation of byproducts (mostly alcohols) limit a wider exploitation of this transformation. In an early report, Cook and coworkers studied the acylation of alkyl Grignard reagents. Different catalysts and reaction conditions were tested; the best results (47% yield) were achieved with FeCl₃ as catalyst. Cason et al. investigated the use of FeCl₃ as catalyst for the coupling reaction of succinyl chlorides with ethylmagnesium bromide at low temperatures (0 to −40 °C). It was demonstrated that the use of FeCl₃ suppressed the formation of alcohol byproducts. A mechanism that seems to be consistent with the experimental observations is shown in Scheme 26.
In 1996 Reddy and Knochel discovered that diorganozinc compounds are another class of competent nucleophiles that undergo facile acylation with acyl chlorides in the presence of catalytic FeCl₃ (10 mol %) in THF/NMP at 80°C. Förstner and coworkers disclosed the rapid reaction of functionalized acid chlorides with various alkyl and aryl magnesium halides to give ketones in good yields at 78°C (<15 min). The iron-catalyzed reaction of acyl chloride is faster than the cross-coupling of aryl halides. Aryl chlorides and bromides thus do not interfere (Scheme 30).[27]

Especially the “inverse addition” (the acyl chloride is added to a cold solution containing Fe(acac)₃ and the Grignard reagent) has attracted particular attention because the uncatalyzed attack of the Grignard reagent onto the resulting ketone is negligible.[29] Simultaneously, Knochel and coworkers devised a strategy to build polyfunctionalized diarylketones by Fe(acac)₃-catalyzed arylation of aroyl cyanides. The procedure tolerates aryl chlorides, esters, and ethers (Scheme 31).[57]

The methylthation of an acyl chloride in the total synthesis of Lantrunculin B (Scheme 29).[28]

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Cross-Coupling with Aryl Electrophiles

Alkyl Metal Nucleophiles

In 1989, Pridgen et al. revealed the superiority of Fe(acac)₃ to Ni(acac)₂ in the cross-coupling reaction of ortho-halobenzaldehydes with “reducing” Grignard reagents (i.e., bearing β-hydrogen atoms).[58] The iron-catalyzed reaction was not accompanied by the formation of reductive byproducts (Scheme 32).

Förstner et al. developed general conditions for cross-coupling reactions of alkyl and aryl metal species (Mg, Zn, Mn) with aryl and heteroaryl chlorides, triflates, and tosylates (Scheme 33).[8,59,60] Unlike aryl chlorides, the corresponding bromides and iodides were prone to reduction of the C–X bonds. The wide substrate scope involved functionalized aromatic compounds bearing ether, sulfonate, nitrile, or heterocycle substituents. Alkylmagnesium substrates containing alkene or alkyne moieties were also competent reactants. Both [Fe(salen)Cl] and Fe(acac)₃ proved equally active, while the former exhibited superior activity with secondary Grignard reagents.
The versatility of this protocol was demonstrated by several total syntheses, for example, macrocyclic spermidine alkaloid lisoconinotine[59], cytotoxic marine natural product Montipyridine, and immunosuppressive FTY720 (Scheme 34). [60] Förster and coworkers proposed a mechanism rationale for iron catalyzed cross-coupling reactions between aryl halides and alkylmagnesium halides. In accordance with previous reports by Bogdanovic and Schwickardi, [61] a formal Fe(MgX)₂ species was postulated to act as catalytically active low-valent catalyst. This highly nucleophilic species, an “inorganic Grignard compound” with iron formally in oxidation state −2, is believed to undergo oxidative addition with aryl halides resulting in an aryliron intermediate, which is subject to alkylating transmetallation from the Grignard reagent. Subsequent reductive elimination of the two organic moieties releases the cross-coupling product and regenerates the catalytically active iron species (Scheme 35). [60a, 62] The exceptional efficiency of this aryl–alkyl cross-coupling methodology was demonstrated in the total synthesis of (R)-(−)-Muscopryridine by Förster and Leitner (Scheme 36). [63]

In similar fashion, Nagano and Hayashi exploited such methodology for the functionalization of aryl triflates. [64] The group of Hocek studied the methylation of 2,6-dichloropurines and 6,8-dichloropurines via iron-catalyzed cross-coupling reaction with methylmagnesium halides and established a novel approach toward 2-chloro-6-methylpurine and 6-chloro-8-methylpurine (Scheme 37). [65, 66] Reactions with trichloro-substituted purines revealed a rather unselective course of the coupling reaction as mixtures of mono-, di-, and trimethylated products were obtained. [66] Schulz and coworkers synthesized a series of substituted pyrazines, which have also been found in marine bacteria, from 2-chloropyrazines. [67]

Selective iron-catalyzed mono-substitutions of dichloro-substituted arenes and heteroarenes in good yields were also reported by Förster and coworkers (Scheme 38). Reactions with ortho-substituted substrates, however, were sluggish. [27]

**Aryl Metal Nucleophiles**

![Scheme 33. Iron-catalyzed aryl-alkyl coupling reaction by Förster et al.][60a]

![Scheme 34. Cross-coupling in the total synthesis of Montipyridine.][60]

![Scheme 35. Simplified Fe−based mechanism by Förster and coworkers.][34, 62]

![Scheme 36. Consecutive coupling reactions toward (R)-(−)-Muscopryridine.][63]

![Scheme 37. Selective iron-catalyzed methylation of 2,6-dichloropurine.][64a]

![Scheme 38. Aryl Metal Nucleophiles][27]
The iron-catalyzed homo-coupling of aryl Grignard reagents with bromobenzene as oxidant was described already by Kharasch and Fields in 1941. Phenylmagnesium bromide was reacted with bromobenzene in refluxing diethylether producing biphenyl within 1 h in 47% yield (Scheme 39). A related homo-coupling procedure was described by Felkin and Meunier when phenyl magnesium bromide was treated with benzyl chloride in the presence of iron catalysts. Minor formation of the cross-coupling product was also observed.

In 2002, Fürstner and Leitner reported that cross-coupling products of heteroaromatic chlorides with aryl Grignard reagents can be obtained in high yields by using catalytic Fe(acac)₃ in a solvent mixture of THF and NMP at 0°C. Noteworthily, electron-rich aryl halides tended to fail, giving merely homo-coupling of the arylmagnesium species. With this system it is also possible to couple chlorides of various π-electron-deficient heteroaromatic systems such as pyrimidine, pyrazine, triazine, isoquinoline, quinazoline, and quinoxaline with 3-pyridylmagnesium bromide or 2-thienylmagnesium bromide in moderate yields without using NMP as co-solvent (Scheme 40). Sterically demanding Grignard reagents were unreactive. Later, Fürstner et al. proved the inactivity of Fe(salen)Cl catalysts for such protocols.

Later, Knochel and coworkers showed that iron powder also efficiently catalyzes this transformation. The cross-coupling product was obtained after 12 h at ambient temperature in 86% yield (Scheme 43). This result supports the consideration that a reduced (ferrate) species might act as active catalyst.

Figadère and coworkers tested various solvents and additives for the coupling of 3-bromoquinoline and 2-bromoquinoline with phenylmagnesium bromide in the presence of catalytic amounts of iron salts under various conditions (Scheme 41). Highest yields were achieved with a simple protocol involving 10 mol% Fe(acac)₃ in THF at −30°C and 1 h reaction time.

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Plé and coworkers reported that iron-catalyzed cross-coupling reactions of pyridine or diazine chlorides with aryl Grignard reagents allow the synthesis of various unsymmetrical polyaryl or polyheteroaryl compounds with π-deficient rings (Scheme 42).

Later Knochel and coworkers showed that iron powder also efficiently catalyzes this transformation. The cross-coupling product was obtained after 12 h at ambient temperature in 86% yield (Scheme 43). This result supports the consideration that a reduced (ferrate) species might act as active catalyst.

In 2004 Nagano and Hayashi reported on a novel methodology for the homo-coupling of various aryl Grignard reagents using FeCl₃ as a catalyst precursor and 1,2-dichloroethane as
oxidant in refluxing diethyl ether. This reaction system was readily amenable to a variety of aryl halides (aryl chlorides were not reactive) and large-scale syntheses of the resultant biaryl compounds. The best results were achieved with para-substituted compounds, whilst ortho-substitution led to lower yields and longer reaction times. According to the proposed mechanism, FeCl₃ reacts with the Grignard reagent to form a low-valent iron complex A (Scheme 44). Oxidative addition of 1,2-dichloroethane to A gives alkyliron intermediate B which upon β-halogen elimination and ethylene evolution gives dihiloiron species C. Subsequently, transmetalation of the aryl group affords a diaryliron intermediate D which undergoes reductive elimination of the homo-coupling product and regenerates catalyst A.

Cahiez et al. optimized this transformation and showed that the reaction can be performed with only 0.6 eqs. of 1,2-dichloroethane. Reactions of ortho-substituted aryl Grignard reagents were significantly accelerated when using 1,2-dibromo- or 1,2-diodoethane as reoxidants. The authors extended the procedure to also include highly functionalized substrates with ester, nitrile, and nitro groups. Accordingly, the total synthesis of N-methylcrinasiadine was achieved via iron-catalyzed intramolecular cross-coupling reaction (Scheme 45).

Knochel and coworkers demonstrated that the homo-coupling reaction pathway can be suppressed if the Grignard reagent is transmetalated to the corresponding organocopper species. This procedure allows for cross-coupling of aryl and heteroaryl compounds in high yields (Scheme 46). Some general trends in the reactivity were observed: (a) electron-withdrawing groups at the aryl iodide accelerate the cross-coupling, (b) the reaction proceeds slower in the presence of electron-donating groups, (c) the rate of the reaction depends also on the leaving group: I > Br > Cl > OTf (tosylates were unreactive), and (d) 2- and 4-iodobenzoates react significantly faster than the 3-isomer. The mild reaction conditions tolerate esters, ketones, ethers, acetics, alkylsilanes, nitriles, and amides.

Homo-coupling of arylbromides was reported by Pei and coworkers to proceed with catalytic Fe(dbm)₃ and 2 equivalents of magnesium with good yields. In 2007, Hatakeyama and Nakamura delivered a novel catalytic system for the hetero-biaryl coupling based on FeF₃·3H₂O and SIPrHCl (1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride). The presence of NHC as ligand and fluoride counteranion proved critical for high selectivities and led to the suppression of homo-coupling products (Scheme 47). The procedure is tolerant of dimethylamino, methylthio, fluoro, and acetal functionalities. Various aryl Grignard reagents can be used, although sterically hindered ones reacted slower. A vast array of aromatic and heteroaromatic halides were also tested, following the general trend Cl > OTf > Br > I.
A study by Young and coworkers disclosed a positive influence of high pressure (15 kbar; 1 bar = 10^5 Pa) in the liquid phase on the Suzuki–Miyaura cross-coupling of aryl halides and aryl boronic acids catalyzed by cheap metal salts (NiCl₂, CoCl₂, FeCl₃) in the presence of dppy as ligand (Scheme 48).

Small amounts of biphenyl arising from boronic acid homocoupling were formed along with the cross-coupling product. It was postulated that the primary effect of the pressure is the acceleration of the reduction of the metal to a catalytically active oxidation state.[78]

Franzén and coworkers have exploited a stable tetrakis(pyridine)iron(II) catalyst for Suzuki-type biaryl forming reactions (Scheme 49). Functionalized aryl bromides (NO₂, COMe, OMe) can be reacted with phenylboronic acid in good yields in an aerobic atmosphere and aqueous ethanol (1:1) at low catalyst loadings (1 mol %). Addition of TBAB was found to increase the yield of the biaryl.[79]

Iron-Catalyzed Sonogashira Reactions[80]

In 2008, the range of applications of iron catalysts to cross-coupling reactions was significantly broadened by a publication from the group of Bolm, which developed a novel iron-catalyzed arylation of terminal alkynes. With catalytic amounts of FeCl₃ and N,N'-dimethylethylenediamine (dmeda) as ligand, various electron-rich and -deficient aryl iodides furnished the desired arylacetylenes in good yields. The scope of the reaction is limited to aryl iodides. Aryl tosylates and bromides turned out to be significantly less reactive and gave only traces of or no coupling product (Scheme 50).[81]

A related ligand-free iron–copper-co-catalyzed cross-coupling reaction of aryl halides with terminal alkynes was recently reported by the group of Mao. While aryl iodides provided the corresponding coupling products in good yields (up to 99 %, see Scheme 51), iodine (10 mol %) as additive was required in the case of aryl bromides in order to achieve moderate yields of the alkylation products. The same protocol was also applied to C–O and C–S coupling reactions with good yields.[82]

Cross-Coupling with Alkyl Electrophiles

In 2008, the range of applications of iron catalysts to cross-coupling reactions was significantly broadened by a publication from the group of Bolm, which developed a novel iron-catalyzed arylation of terminal alkynes. With catalytic amounts of FeCl₃ and N,N'-dimethylethylenediamine (dmeda) as ligand, various electron-rich and -deficient aryl iodides furnished the desired arylacetylenes in good yields. The scope of the reaction is limited to aryl iodides. Aryl tosylates and bromides turned out to be significantly less reactive and gave only traces of or no coupling product (Scheme 50).[81]
Cossy and coworkers carefully studied reaction conditions for the cross-coupling of vinyl Grignard reagents with primary and secondary alkyl iodides and bromides. While the standard Fe(acac)₃/THF/NMP protocol failed, the FeCl₃/TMEDA system afforded the anticipated products in high yields (>90%). Slow addition of the Grignard reagent/TMEDA mixture to the FeCl₃/substrate solution was crucial for high conversions. These conditions were, however, not applicable to aromatic halides and α- or β-bromo esters. The reactions of secondary halides were accompanied by the formation of elimination products (Scheme 53). Simultaneously, Cahiez et al. also realized an efficient coupling between alkenyl Grignard reagents and primary or secondary alkyl halides using a Fe(acac)₃/TMEDA/HMTA (1:2:1) catalyst system in THF. While the reaction of alkyl iodides and bromides proceeded smoothly, the corresponding chlorides reacted only sluggishly, giving low yields. The procedure is tolerant of ester and nitrile functions. The reaction was highly chemo- and stereoselective (E/Z ~ 85:15). Selected examples of direct cross-coupling reactions between vinyl bromides and alkyl bromides were reported by Jacobi von Wangelin and coworkers as part of a study on domino iron catalysis involving slow, in situ formation of the Grignard reagent (Scheme 54). Nakamura et al. discovered the beneficial effect of amines (such as TMEDA) on the selectivity of aryl–alkyl cross-coupling reactions in THF at –78 °C with FeCl₃ as catalyst. Highly selective cross-coupling reactions of primary and secondary alkyl halides with minimal competing elimination required slow addition of the aryl Grignard reagent (Scheme 55). Certain trends in the reactivity of alkyl halides were observed (I > Br > Cl, electron-rich > electron-poor Grignard reagents). Mechanistic studies led to the assumption that a bulky “iron-bound radical” intermediate acts as catalyst as it was suggested for the iron-catalyzed living radical polymerization.

Nakamura et al. later expanded the scope of this procedure to arylzinc reagents. The presence of a magnesium salt (as byproduct of the Mg-to-Zn transmetalation) was shown to be mandatory for the successful course of the cross-coupling reaction (yields ca. 90%, Scheme 56). With organozinc species, no slow addition of the organometallic was required.

Fürstner and coworkers investigated the competence of the well-defined complex [Li₂(tmeda)][Fe(C₂H₄)₄], a ferrate(−II) complex in which iron exhibits d⁰ configuration, as cross-coupling catalyst. It could be prepared upon successive removal of the cyclopentadienyl rings from ferrocene under reducing con-
ditions in the presence of pressurized ethylene and related to the investigations into subvalent iron-olefin complexes pioneered by Jonas et al.\textsuperscript{[34, 92]} It was shown that primary alkyl iodides, secondary alkyl bromides, and propargyl and allyl halides reacted smoothly with aroyl Grignard reagents, affording the desired arylated products in virtually quantitative yields in most cases (Scheme 57). Tertiary halides and alkyl chlorides were found to be inert. The obtained results suggest that Fe\textsuperscript{II} species, such as the elusive \([\text{Fe}(\text{MgX})_2]\),\textsuperscript{[60a, 61, 62]} could be the catalytically active species in iron-catalyzed cross-coupling reactions between organohalides and organomagnesium compounds. A radical mechanism, however, cannot be ruled out because radical clock experiments with 6-bromo-hexene exhibited intramolecular ring closure rather than cross-coupling.\textsuperscript{[93]}

Bedford et al. tested easily accessible iron(III)-salen complexes in reactions of primary and secondary alkyl halides bearing \(\beta\)-hydrogens with aryl Grignard reagents. The cross-coupling products were obtained in modest to good yields (Scheme 58).\textsuperscript{[94]} Similarly, Nagano and Hayashi discovered that primary and secondary alkyl bromides efficiently react with aryl Grignard reagents in the presence of catalytic Fe(acac)\textsubscript{3} in refluxing diethyl ether.\textsuperscript{[64]} Diethyl ether seemed to be more efficient than THF or THF/NMP mixtures, as competitive \(\beta\)-hydride elimination and reduction were minimized. The protocol is not suitable for tertiary halides and triflates, allowing chemoselective transformations (Scheme 59).

Bedford et al.\textsuperscript{[95]} and Kozak and coworkers\textsuperscript{[96]} proved that mixtures of iron(III) chloride and appropriate amine ligands are active catalysts for the coupling of aryl Grignard reagents with primary and secondary alkyl halide substrates bearing \(\beta\)-hydrogens (Scheme 60). FeCl\textsubscript{3}/triethylamine seemed to be optimal for the consumption of sterically hindered alkyl halides under mild conditions, while sterically hindered Grignard species failed to react. The use of FeCl\textsubscript{3}/DABCO led to the highest E/Z selectivities and was most effective for less hindered halides. In contrast to the aforementioned results by Nakamura et al.,\textsuperscript{[88]} the FeCl\textsubscript{3}/TMEDA system fared least well in most reactions.

In a concise study by Bedford et al., alternative catalyst systems with phosphane, phosphite, arsine, or NHC ligands have also been subjected to aryl-alkyl cross-coupling reactions and proved similarly active (Scheme 61).\textsuperscript{[93a]} Better conversions to the desired products were typically attained with alkyl bromides independent of the choice of catalyst. The general trend appeared to be \(\text{Br} > \text{I} > \text{Cl}\). The same group also performed mechanistic studies on the model reaction of phenylmagnesium bromide with (bromomethyl)cyclopropane and postulated a plausible radical pathway (Scheme 62). The active low-valent iron species in oxidation state \(n\) is believed to react with the alkyl halide via a single-electron-transfer process to give an alkyl radical/[Fe\textsuperscript{+1}/X] pair. Transmetalation of the aryl moiety...
from the Grignard reagent generates an iron-aryl complex, which eliminates the coupling product. It was also shown that the active iron species might also include nanoparticles stabilized by additives such as poly(ethylene glycol).\(^{[93b]}\)

Bedford et al. efficiently applied 1,2-bis(diphenylphosphino)benzene as ligand for the iron-catalyzed Negishi-type coupling of arylzinc reagents with benzyl halides and phosphates. The remarkable tolerance of halides on the benzyl ring allows selectivities that cannot be realized by analogous palladium catalysis.\(^{[97]}\) Bica and Gaertner introduced a novel catalyst system. The ionic liquid \(n\)-butylmethylimidazolium tetrachloro-ferrate (bmim-FeCl\(_4\)) was found to be a highly effective and completely air-stable catalyst for the biphasic cross-coupling reaction of primary and secondary alkyl halides bearing \(\beta\)-hydrogens with arylmagnesium halides (Scheme 63).\(^{[98]}\) Moreover, the iron catalyst was successfully recycled and reused multiple times. An increased reactivity of electron-poor Grignard reagents was observed. Attempts to use tertiary alkyl halides or aryllithium reagents failed.

Cahiez et al. disclosed two efficient ecofriendly iron-catalyzed procedures to couple secondary and primary alkyl halides (Br, I) with aromatic Grignard reagents using two novel catalytic systems: \([\text{Fe(acac)}_3]/\text{HMTA/TMEDA} (1:1:2)\) and the complex \([\text{[FeCl}_3]_2\text{(tmeda)}_3]\).\(^{[99]}\) A large excess of TMEDA typically used under conventional conditions could be thus reduced to catalytic amounts (Scheme 64). The authors suggested that the iron-catalyzed reaction commences with an oxidative addition of the alkyl halide to a nucleophilic bisaryliron(0) complex via a single-electron transfer (Scheme 65). Secondary and primary alkyl bromides were used successfully in cross-coupling reactions, with the former giving higher yields.

Rao Volla and Vogel disclosed reaction conditions for the desulfenylationative C–C cross-coupling of alkylsulfonyl chlorides with Grignard reagents using Fe(acac)\(_3\) as catalyst and NMP as co-solvent (Scheme 66).\(^{[46]}\)

In 2009, Jacobi von Wangelin and coworkers reported on the first direct cross-coupling reaction between aryl halides and alkyl halides in the presence of metallic magnesium and iron/amine catalyst. The reaction involves in situ formation of catalytic systems: \([\text{Fe(acac)}_3]/\text{HMTA/TMEDA} (1:1:2)\) and the complex \([\text{[FeCl}_3]_2\text{(tmeda)}_3]\). A large excess of TMEDA typically used under conventional conditions could be thus reduced to catalytic amounts (Scheme 64). The authors suggested that the iron-catalyzed reaction commences with an oxidative addition of the alkyl halide to a nucleophilic bisaryliron(0) complex via a single-electron transfer (Scheme 65). Secondary and primary alkyl bromides were used successfully in cross-coupling reactions, with the former giving higher yields.
the Grignard reagent and subsequent rapid cross-coupling. The authors also elucidated a novel iron-catalyzed Grignard formation and demonstrated the concept of domino iron catalysis in cross-coupling reactions (Scheme 67). The reaction conditions of the underlying one-pot reaction are highly sustainable as they preclude the utilization of hazardous Grignard reagents and limit the amount of reactive organomagnesium intermediates to low quasi-stationary concentrations. [87]

Alkylmagnesium Nucleophiles

The seminal investigations into iron-catalyzed cross-coupling reactions between alkyl halides and alkyl Grignard reagents by Kochi et al. revealed that significant amounts of coupled products can only be obtained when the alkyl group is devoid of any β-hydrogen atoms, as in methyl, neopentyl, phenyl, or benzyl moieties.[12] In all other cases, disproportionation was operative and β-hydride elimination products were mainly obtained. Experiments with radical scavengers such as styrene led to inhibition of the cross-coupling reaction and suggest the operation of a radical mechanism. Later, Kochi’s protocol was optimized for the coupling of gem-dichlorocyclopropanes with methyl magnesiumbromide by the group of Tanabe. Various iron precatalysts and additives were screened and the combination of Fe(dmb)₃ (5 mol%) with 4-methoxytoluene or p-xylene was identified to be most efficient (Scheme 68).[100]

Reaction conditions for the sp³–sp³ cross-coupling between alkyl Grignard reagents and unactivated primary or secondary halides were delivered by Chai and coworkers.[101] Based on the extensive screening of different ligands, iron sources, and solvents, Fe(OAc)₃ in combination with bidentate phosphine ligand Xantphos in DME at ambient temperature proved to be most effective (Scheme 69). Yields up to 64% were achieved with primary bromides; secondary bromides afforded up to 43% of the long-chain alkanes. Mechanistic investigations revealed that the reaction of alkyl Grignard reagents with 6-bromohex-1-ene mostly led to cyclization, suggesting a radical pathway.

Allyl and Propargyl Electrophiles

Allenes are versatile building blocks for advanced organic synthesis because of the reactivity inherent to their axially chiral backbone. They are usually prepared by S_n2 reaction of propargylic systems with organocuprates. In 1976, Pasto et al. discovered that primary and secondary Grignard reagents can be reacted with terminal and internal propargyl halides in the presence of catalytic FeCl₃ in a highly selective fashion, affording allenes in yields up to 90%. Reductive formation of only small amounts of alkynes and conjugated dienes was observed (Scheme 70).[102] A mechanism for this tandem reaction of π-rearrangement and cross-coupling was proposed.[103]

Hashmi and Szeimies studied related reactions with tricyclo-[4.1.0.0]hept-1-yl Grignard reagents and propargylic and allylic halides.[104] Fe(acac)₃ is a competent catalyst for the formation of allyl, allenyl, and propargyl-substituted bicyclo-[1.1.0]butanes in moderate yields and high purity while Ni(acac)₃ and
CoCl₂ appeared to be less effective. Stereo-electronic factors were exploited to govern the course of the reaction for the preparation of either propargylic or allenylic products (Scheme 71).

Similar reactions for the preparation of chiral allenes were investigated by Mendéz and Fürnster. Enantiomerically enriched propargyl epoxides could be efficiently converted into the corresponding 2,3-allenols upon iron-catalyzed reaction with Grignard reagents.\(^{[105]}\) Fe\((acac)_3\) (5 mol%) was used as catalyst and the central chirality of the substrates was transferred to the axial chirality of the products with high fidelity (Scheme 72). No additional ligands were required, the yields were good to excellent, and the substrate scope sufficiently broad. Attempts with propargyl halides, however, resulted in low yields and enantioselectivities. Fürnster et al. also applied this methodology in the total synthesis of Amphidinolides X and Y.\(^{[106]}\)

Yamamoto and coworkers showed that the treatment of primary allylic phosphates with allyl, aryl, propargyl, or vinyl Grignard reagents in the presence of 5 mol% Fe\((acac)_3\) at −70 °C in THF resulted in the formation of cross-coupling products in a highly chemoselective manner (yields 70–90%, selectivity < 98:1, Scheme 73).\(^{[107]}\)

Grignard reagents with 5 mol% Fe\((acac)_3\) in the presence of THF resulted in the formation of cross-coupling products in a highly chemoselective manner (yields 70–90%, selectivity < 98:1, Scheme 73).\(^{[107]}\)

Arylative and alkenylative iron-catalyzed ring-opening reactions of [2.2.1.]- and [3.2.1]-oxabicyclic alkenes with Grignard reagents were observed by Nakamura et al. to proceed with high regio- and stereocontrol (Scheme 74).\(^{[108]}\)

Early studies by Roustan and coworkers, Ladoulis and Nicholas, and Xu and Zhou documented the catalytic activity of iron carbonyl complexes in allylic substitution reactions.\(^{[109]}\) In 2006, Plietker published an efficient, salt-free, regioselective iron-catalyzed allylic alkylation of allyl carbonates.\(^{[110]}\) Small amounts of PPh₃ led to a significant increase of the amount of substitution product (Scheme 75). Reactions with enantiopure carbonates suffered a slight decrease of the enantiomeric excess. Later Plietker also proposed a mechanism for such iron-catalyzed al-
lyllic substitutions involving a ligand-dependent dichotomy. Åkermark and Sjögren disclosed a protocol for the substitution of allylic acetate by diethyl methylmalonate with catalytic Fe₂(CO)₉ and dimethylamine.

**C–H Functionalization**

Transition-metal-catalyzed C–H activation has recently gained considerable momentum and is now widely recognized for its potential to form a host of C–C and carbon–heteroatom bonds in an inherently benign fashion. These challenging transformations are currently dominated by expensive metal catalysts based on palladium, rhodium, or ruthenium. The development of efficient iron catalysts for selective C–C bond forming reactions that involve C–H activation are still limited to activated substrates (proximal heteroatom or directing group) while several methods exist for oxidations of C–H bonds with iron catalysts. Nakamura and coworkers developed an iron-catalyzed C–C bond-forming reaction through initial C–H bond activation. Accordingly, α-benzoquinoline and related heterocyclic structures can be reacted with arylzinc reagents at remarkably low temperatures (0 °C). The protocol requires a large excess of the Grignard reagent and the ZnCl₂·TMEDA complex (Scheme 76).[115] Li et al. demonstrated that iron carbonyls are effective catalysts for the selective activation of C–H bonds adjacent to heteroatoms for subsequent C–C bond formation (Scheme 77).[116]

A striking example of an efficient intermolecular iron-catalyzed 1,4-addition of α-olefins to 1,3-dienes was reported by Ritter and coworkers in 2009 (Scheme 78). The catalytically active species is formed upon reduction of FeCl₂ with Mg in the presence of an iminopyridine ligand. The resultant dienes were found to be formed with high stereoccontrol upon stereoselective syn-β-H₂-elimination from an intermediate alkyliron species.[117]

**Heck-Type Reactions**

An isolated example of an iron-catalyzed Heck reactions has so far been reported by Vogel and coworkers. In the presence of a rather large amount of FeCl₂ (20 mol%), picolinic acid as ligand (80 mol%), and KOtBu as base (4 eqs.) substituted styrenes can be obtained from reaction of aryl and heteroaryl iodides with styrenes in DMSO in moderate to good yields (Scheme 79).[118]

**Summary and Outlook**

Iron-catalyzed cross-coupling reactions have matured to an advanced stage and provide synthetic organic chemists with a versatile arsenal of C–C and C–X bond-forming methods. With highly reactive iron catalysts, reactions of substrates usually considered cumbersome under palladium and nickel catalysis, such as secondary alkyl halides, become feasible. The high reactivity is inherited from the presence of organomagnesium species that are (a) crucial for the in situ generation of highly electron-rich iron complexes by reduction of commercial
iron(II) or iron(III) salts, and (b) constitute a strong nucleophile for the cross-coupling step. Combinations of iron salts and amine ligands, which are the most prevalent type of catalyst system, allow for mild reaction conditions and a large range of applications owing to their high reactivity towards various classes of electrophiles and organomagnesium compounds. General protocols for cross-coupling reactions with various alkyl-, alkenyl-, and aryl-MgX nucleophiles have been developed. However, the design of competent catalysts and reaction conditions for alkyl-alkyl cross-coupling is still at an early stage and remains a true challenge. Improvements with regard to functional group compatibility are clearly desirable. Another aspect that is closely linked to the use of Grignard reagents revolves around the required operational safety arrangements. The hazard potential of organomagnesium halides (e.g., flammable, corrosive, moisture- and air-sensitive) entails additional cost-intensive measures that might limit industrial realizations on larger scales. The overall process simplicity would thus highly benefit from the employment of less-hazardous organo-metallic components or alternative safe or in situ Grignard-formations as found under direct cross-coupling conditions. It is also important to note that the mechanistic details of iron-catalyzed cross-coupling reactions are not fully understood. This is largely due to the fact that structure and property data of low-valent iron or ferric complexes are scarce. The postulated catalytically active iron species are highly reactive and mostly too short-lived for classical direct analytical techniques. It will take extensive and elaborate synthetic efforts to design ligand-stabilized iron complexes that lend themselves to detailed investigations and allow monitoring catalytic intermediates.

Future research will certainly be aimed at the optimization of reaction conditions to attain higher productivity (<1 mol% catalyst) and greater tolerance of sensitive functional groups. Further mechanistic studies are required to establish the identity of catalyst species and intermediates as well as the often unpredictable effects of additives. With regard to efficiency criteria, improvements in atom economy are necessary, as most protocols require an excess of one substrate. The rapid progress of iron-catalyzed cross-coupling reactions that the community has witnessed over the past years encourages us to expect more efficient catalyst systems and reaction conditions to be developed in the near future. Furthermore, if selective (and stereospecific) reactions with sterically hindered secondary and tertiary alkyl halides become generally possible, these methods will undoubtedly become an indispensable part of the organic chemists’ toolbox for sustainable syntheses of complex molecules.

**Abbreviations**

- acac = acetylacetonate
- BOC = t-butyloxy carbonyl
- c-hex = cyclohexyl
- DABCO = 1,4-diazabicyclo[2.2.2]octane
- dbm = dibenzylmethide
- DME = dimethoxyethane
- DMSO = dimethyl sulfoxide
- dppe = 1,2-diphenylphosphinoethane
- dpf = 1,1’-bis(diphenylphosphino)ferrocene
- dpyp = 2-(diphenylphosphino)pyridine
- Hex = n-hexyl
- HMTA = hexamethylenetetramine
- MOM = methoxy methyl
- NHCl = N-heterocyclic carbene
- NMP = N-methyl-2-pyrrolidone
- Oct = n-octyl
- ONF = nonaflate, nonafluorobutanesulfonate
- OTf = triflate, trifluoromethanesulfonate
- 1,10-phen = 1,10-phenanthroline
- PMB = p-methoxy benzyl
- py = pyridine
- SiPHCl = 1,3-bis-(2,6-disopropylphenyl)-4,5-dihydroimidazolium chloride
- TBAB = tetrabutylammonium bromide
- TBDPS = t-butyldiphenylsilyl
- TBDMS = TBS = t-butyldimethylsilyl
- TFA = trifluoroacetic acid
- THF = tetrahydrofuran
- TIPS = triisopropysilyl
- TMEDA = N,N,N’-tetramethylethlenediamine
- Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

**Keywords:** homogeneous catalysis · cross-coupling · Grignard reaction · iron · transition metals

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