Highlight Review

Advances in Iron Catalyzed Cross Coupling Reactions

Alois Fürstner* and Rubén Martin

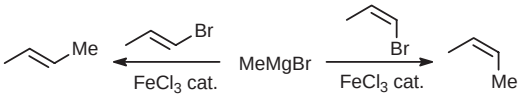
(Received December 20, 2004; CL-048018)

Abstract

This account summarizes recent developments in the use of cheap, benign, and non-toxic iron salts as precatalysts for various cross coupling reactions. Although not yet nearly as mature as their palladium- or nickel-catalyzed counterparts, these transformations provide efficient and scalable solutions for many types of C–C-bond formations. Selected applications to the total synthesis of bioactive natural products illustrate the present state of the art.

♦ Introduction

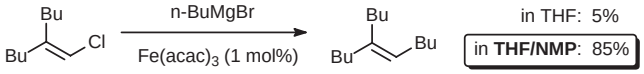
Palladium- and nickel-catalyzed cross coupling reactions are an indispensable tool for organic synthesis.[1] Despite the truly impressive application profile and maturity of this methodology, the search for possible alternatives might be rewarding, provided that catalysts can be found that are similarly effective, yet cheaper and/or less toxic. Early reports by Kochi et al. on the use of iron salts provide a particularly promising lead in this regard.[2] Surprisingly though, this method remained essentially restricted to alkenyl halides, -phosphates, and -sulfones as the substrates for a rather long period of time. Only recently was it possible to extend the scope of iron-catalyzed cross coupling reactions beyond these types of electrophiles and to implement the method into the synthesis of natural products and pharmaceutically relevant targets. These applications are distinguished by the low cost, ready availability, and benign character of the required iron salts as well as by exceptionally high reaction rates and notably mild conditions. Outlined below is an overview over this emerging field, which is limited to iron *catalyzed* processes[3] and does not cover C–C-bond formations involving stoichiometric organoiron reagents.[4]



Scheme 1.

In a series of classical investigations, Kharasch et al. studied the effect of metallic halides on the formation and reactivity of Grignard reagents.[5] These authors noticed that catalytic amounts of $FeCl_3$, $CoCl_2$, $NiCl_2$, $CuCl_2$, or $CrCl_2$ engender a previously unknown "redox catalysis" leading to significant amounts of the *homo*-coupling products of the organomagnesium compound if an organic halide is present in the reaction mixture as a stoichiometric 'oxidant.'

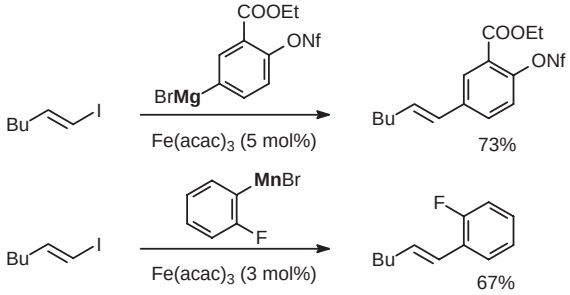
In 1971 Kochi et al. reported a significant advance over this prior art,[2,6] when he noticed that alkenyl halides undergo stereospecific *cross* coupling with alkyl Grignard reagents in the presence of catalytic amounts of FeX_3 with retention of the configuration of the substrate (Scheme 1). Thereby, (*E*)-alkenyl bromides react an order of magnitude faster than their (*Z*)-configured counterparts. By optimizing the solvent and lowering the reaction temperature it was possible to extend this transformation to aryl Grignard reagents as the nucleophiles.[7] However, the fact that the alkenyl halide had to be employed in excess constituted a significant drawback in preparative terms.



Scheme 2.

This limitation was overcome by Cahiez et al. who showed the beneficial effect of NMP as cosolvent in such transformations (Scheme 2).[8,9] Under these conditions, the reactions of alkenyl halides (1 equiv., X = I, Br, Cl) proceed stereo- and chemoselectively even if reactive functional groups such as amides, esters, ketones, and alkyl chlorides are present in the substrates. Further flexibility was gained with the advent of functionalized Grignard reagents.[10,11] A striking example is shown in Scheme 3, in which the alkenyl iodide reacts in high yield with a Grignard reagent bearing an aryl nonaflate (Nf) moiety that remains intact.[12] Moreover, (functionalized) organomanganese derivatives were found to be suitable donors for similar purposes.[9,13]

Alkenyl sulfones[14] and -phosphates[8] (Scheme 4) were also found to be suitable substrates, although formal reduction of the C–X bond occasionally accompanies productive cross coupling. Likewise, allyl phosphates react well in the presence of iron catalysts.[15]



Scheme 3.

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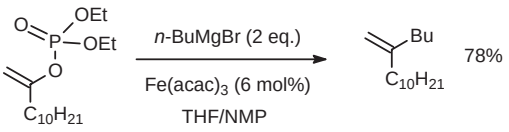


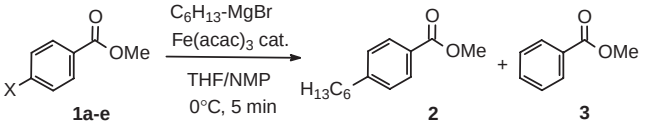
Scheme 4.

♦ A Hypothesis Driven Re-launch

Despite these encouraging results, the mechanism of iron catalyzed cross coupling reactions remained rather obscure. It has been speculated that Fe(0) or Fe(+I) species constitute the catalytically relevant intermediates,[16] while other authors advocated the presence of "super-ate" complexes of Fe(+II).[4]

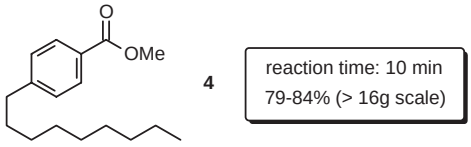
In 2002, we contemplated that recent progress in the seemingly unrelated field of material science might be relevant in the context of iron catalyzed C–C-bond formation. Thus, Bogdanovic et al. have shown that many transition metal halides MX_n react with reducing organomagnesium species to give "inorganic Grignard reagents" of the formal composition $[X_{n-a}M(MgX)_a]$ in which magnesium has formally inserted into one or more M–X bonds.[17] Specifically, $FeCl_2$ reacts with *four* equiv. of RMgX to give a cluster species of the formal composition $[Fe(MgX)_2]$ with release of R–H, the corresponding alkene and the homodimer R–R. This implies that the reduction does not stop once a zerovalent iron species "Fe(0)" is formed, but rather generates Fe(−II) centers which might be able to oxidatively insert into aryl halides owing to their highly nucleophilic character. With this hypothesis in mind, we launched a research program aiming at a re-evaluation of iron catalyzed cross coupling chemistry.[18,19]

Table 1. Effect of the leaving group on the iron catalyzed cross coupling of **1a**–**1e** with *n*-hexylmagnesium bromide

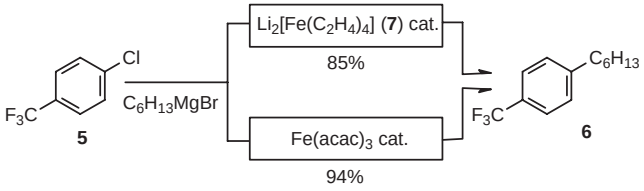


1	X	2 (GC)	3 (GC)
a	I	27%	46%
b	Br	38%	50%
c	Cl	>95%	—
d	OTf	>95%	—
e	OTs	>95%	—

Two key observations were instrumental in this regard. First, we noticed an unexpectedly pronounced effect of the leaving group on the outcome of the reaction (Table 1). Whilst attempted cross coupling of iodide **1a** or bromide **1b** with *n*-hexylmagnesium bromide in the presence of $Fe(acac)_3$ cat. in THF/NMP was rather low yielding and mainly afforded the reduced compound **3**, the corresponding chloride **1c** furnished the desired product **2** in virtually quantitative yield; triflate **1d** and even tosylate **1e** behave similarly well.[18,19] These reactions are exceptionally fast and occur within minutes at or below room temperature as illustrated by the preparation of the liquid crystalline methyl 4-nonylbenzoate (**4**) which was obtained on a >16 g scale within 10 min; a detailed procedure is available from *Organic Synthesis*.[20] This example illustrates that the iron catalyzed activation of the C–Cl bond is much faster than the uncatalyzed attack of the Grignard reagent onto the ester function of the substrate. This favorable kinetic profile translates into an attractive functional group compatibility



The other key observation concerns the nature of the nucleophile. Whilst the iron catalyzed cross coupling of **1c** with *ethyl*magnesium bromide (or higher alkylmagnesium halides) is complete within minutes, *methyl*magnesium bromide essentially fails to react with this particular substrate.[19] Grignard reagents such as phenyl-, vinyl-, or allylmagnesium bromide are also inappropriate and react only in special cases.[19,21] This strikingly different behavior is reflected in a characteristic appearance of the reaction mixtures. Thus, addition of MeLi or MeMgBr to $Fe(acac)_3$ in THF/NMP leads to intensely yellow colored homogeneous solutions likely indicating the formation of the ate complex $[Me_4Fe]M_2$ (M = Li, MgBr),[4a] whereas any alkyl Grignard reagent with ≥2 C-atoms affords dark mixtures containing $[Fe(MgX)_2]_n$ or related cluster species.[21] The distinctly different behavior of MeMgBr is therefore tentatively ascribed to its inability to reduce $FeCl_2$ to $[Fe(MgX)_2]$ by the process described above. Consistent with this notion is the fact that other "non-reducing" carbon nucleophiles such as boronic acids, stannanes and even RZnX or R_2Zn do not engender iron catalyzed cross coupling under the conditions shown in Table 1.[19]



Scheme 5.

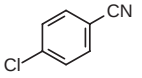
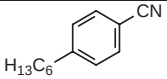
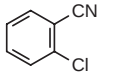
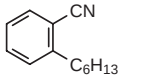
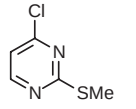
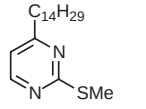
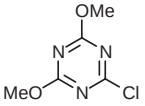
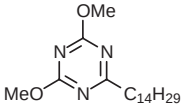
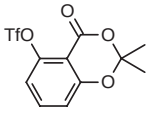
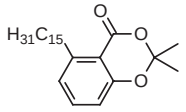
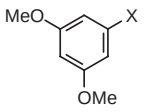
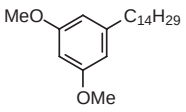
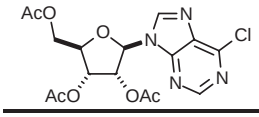
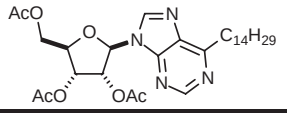
We therefore assume that iron-catalyzed C–C-bond formations can occur via *at least* two different pathways. First, methyl donors and the like are supposed to form "iron–ate" complexes $[R_4Fe]M_2$ which are able to transfer their R groups only to highly activated electrophiles by nucleophilic attack.[21] In contrast, alkyl Grignard reagents with ≥2 carbon atoms likely afford highly reduced metal clusters such as $[Fe(MgX)_2]_n$ which engender a catalytic cycle involving oxidative addition/reductive elimination steps that is much broader in scope.[19,21] Preliminary evidence for this hypothesis comes from control experiments which show that certain structurally well-defined complexes of Fe(−II) are superbly active catalysts for cross coupling reactions of this type.[22] This is particularly true for the complex $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ (**7**) originally prepared by Jonas et al.[23] which presently serves as a model for the "in situ" catalyst in our ongoing mechanistic investigations (Scheme 5).

♦ Scope and Limitations

The iron catalyzed cross coupling of *alkyl* Grignard reagents works exceptionally well for electron deficient aryl- and hetero-

Published on the web (Advance View) March 26, 2005; DOI 10.1246/cl.2005.624

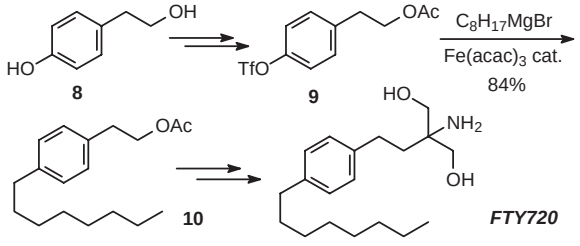
Table 2. Selected examples of iron catalyzed cross couplings of aryl chlorides or -sulfonates and *alkyl*magnesium halides

Substrate	Product	Yield
		91%
		68%
		89%
		84%
		51%
		0% (X = Cl) 90% (X = OTf)
		72%

aryl chlorides and -tosylates as well as for electron rich aryl (heteroaryl) triflates.[18–21] Electron rich aryl chlorides, in contrast, are prone to reduction of the C–Cl bond.[24] Some representative examples for productive C–C-bond formation are compiled in Table 2. The reaction is compatible with esters, ethers, nitriles, sulfonates, sulfonamides, thioethers, acetals, alkynes, and $-CF_3$ groups. It is, however, rather sensitive to steric hindrance in the substrates as evident from the comparison of aryl chlorides (triflates) bearing *ortho* substituents, all of which give (much) lower yields than their *para*-substituted congeners. As discussed above, MeMgBr as well as ArMgX react only with highly activated substrates, most likely owing to a switch in mechanism.[21,25,26]

♦ *Target Oriented Syntheses*

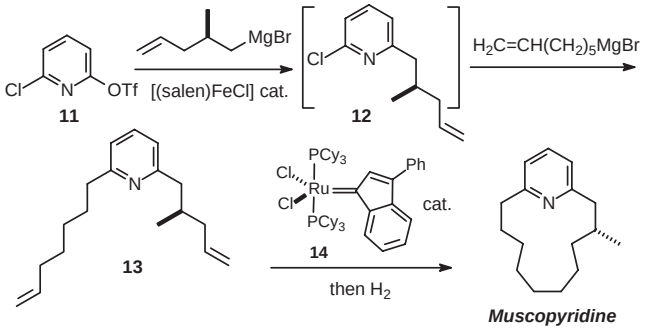
A synthesis of FTY720, a very promising immuno-modulatory agent presently in phase III clinical trials, illustrates some of the advantages associated with the iron-based alkyl–aryl cross coupling chemistry.[27] Specifically, treatment of the readily available triflate **9** with octylmagnesium bromide in the presence



Scheme 6.

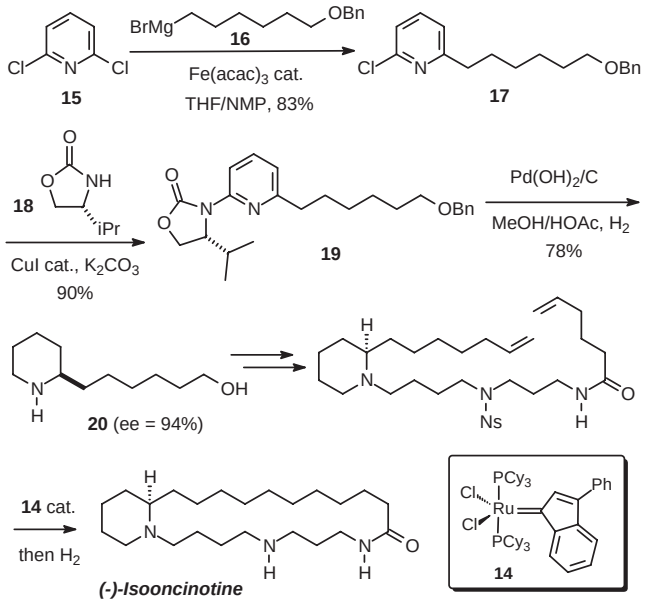
of $Fe(acac)_3$ cat. afforded compound **10** in 84% yield as the key building block for the preparation of this target (Scheme 6). As expected, the reaction is fast, compatible with the acetate protecting group, and easily performed on a multigram scale.[27]

Another notable advantage is the possibility to perform either exhaustive, selective, or sequential cross coupling reactions of arenes bearing more than one leaving group X. This aspect is evident from a highly integrated approach to the musk-odored alkaloid muscopyridine which is based upon the formation of diene **13** by sequential addition of two different Grignard reagents to the bifunctional pyridine derivative **11** (Scheme 7).[28] The triflate in **11** reacts first, followed by cross coupling of the remaining chloride function in intermediate **12** upon addition of the second alkyl Grignard reagent. Although some of the symmetrical diene derived from concomitant activation of the –OTf and –Cl groups is formed as a minor byproduct in the first step, this compound was conveniently removed by a subsequent 'one-pot' ring closing alkene metathesis/ADMET/hydrogenation manifold, thus making cumbersome purification steps unnecessary.[28]



Scheme 7.

An enantioselective synthesis of the spermidine alkaloid (−)-isooncinotine showcases a selective functionalization of a dichloroarene (Scheme 8).[29] In the event, slow addition of the



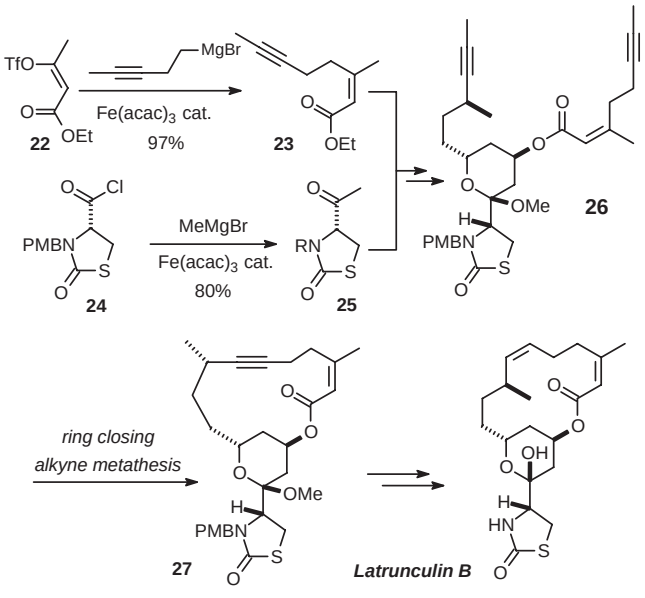
Scheme 8.

functionalized Grignard reagent **16** to substrate **15** in the presence of $Fe(acac)_3$ cat. provided the *mono*-substitution product **17** in 83% yield. Subsequent copper catalyzed replacement of the remaining chloride by the oxazolidinone **18** gave product **19** which was hydrogenated in HOAc over Pd/C to give piperidine **20** in optically active form (ee = 94%). In this key transformation the auxiliary does not only control the configuration of the newly formed chiral center but is also tracelessly removed.[30] Elaboration of compound **20** into isooncinotine again involved an integrated 'one-pot' RCM/hydrogenation step to forge the saturated macrocycle using the readily available ruthenium indenylidene complex **14** as the precatalyst of choice.[31,32]

♦ Increasing the Substrate Range

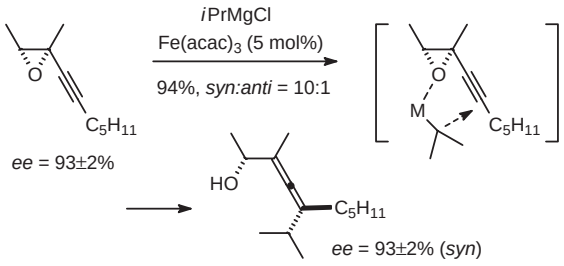
Iron catalyzed cross coupling reactions of Grignard reagents are by no means limited to aryl chlorides and -sulfonates, but work similarly well with a variety of other electrophiles. Thus, alkenyl triflates cross couple with RMgX of various types,[21,33] including even MeMgBr and related donors which likely react via 'iron–ate' complexes of the type $[Me_4Fe]M_2$ (M = Li, MgBr) mentioned above.

Likewise, acid chlorides[21,34] and acyl cyanides[35] are well behaved reaction partners, affording the corresponding ketones in high yields. Not only is a variety of functional groups compatible, but also chiral centers α to the –COCl group are preserved under the chosen conditions.[21] These methods were successfully implemented into a recent total synthesis of the actin binding macrolide latrunculin B using ring closing alkyne metathesis (**26** → **27**) followed by Lindlar reduction as a means to forge the macrocyclic (*Z*)-alkene in an efficient and stereoselective manner (Scheme 9).[36,37]



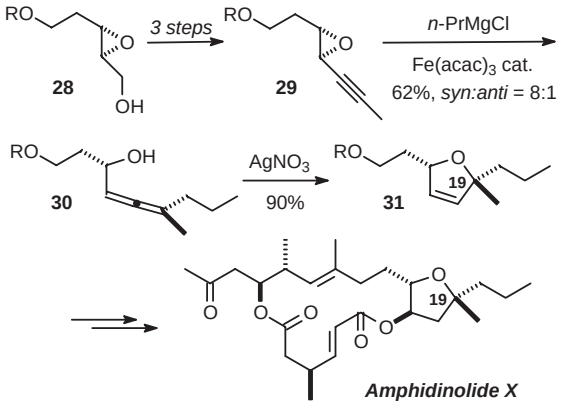
Scheme 9.

Propargyl epoxides constitute yet another class of electrophiles amenable to iron catalyzed C–C-bond formations.[38] On exposure to Grignard reagents they afford the corresponding allenol derivatives under notably mild conditions (Scheme 10). The major isomer is *syn*-configured, most likely owing to a directed delivery of the nucleophile to the alkyne. This outcome nicely complements reactions of propargyl epoxides with organocopper derivatives (which furnish the *anti*-configured allenols) and is best explained by assuming a pre-coordination of the catalyst and/or the Grignard reagent to the oxygen atom of the substrate. Thereby, the central chirality of the epoxide is translated into the axial chirality of the allene with high fidelity. Direct attack of the nucleophile to the oxirane ring remains insignificant in all but the most activated cases.[38]



Scheme 10.

This transformation served as a key step in a recent total synthesis of amphidinolide X, a potent cytotoxic macrolide of marine origin (Scheme 11).[39] Specifically, allenol **30** was used as a relay to build the tertiary ether center at C-19 in enantiomerically pure form from epoxide **29** which is readily obtained by a Sharpless epoxidation strategy.



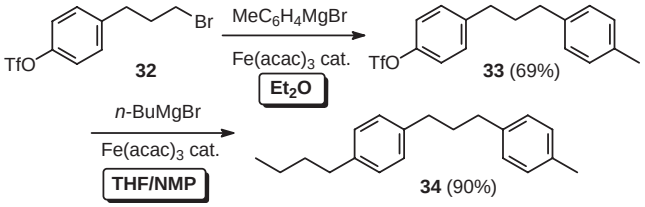
Scheme 11.

♦ Cross Coupling of Alkyl Halides

In contrast to the established palladium or nickel catalyzed cross coupling reactions of aryl and vinyl halides,[1] it was only recently that extensions of this chemistry to alkyl halides as the substrates have been possible.[40] The use of special ligands as well as a careful optimization of the reaction conditions were necessary to overcome the inherent reluctance of alkyl halides to undergo oxidative addition and to suppress the proclivity of the resulting alkyl metal reagents for destructive β-hydride elimination. Therefore it is somewhat surprising that a series of recent publications has shown beyond doubt that bare iron catalysts are able to promote the cross coupling of alkyl halides with ArMgX reagents with remarkable efficiency.

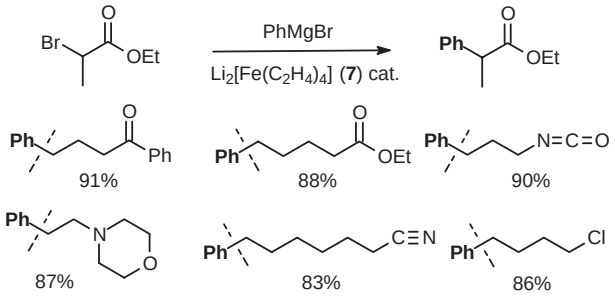
Specifically, Nakamura et al. have successfully cross coupled aryl Grignard reagents with a variety of primary and secondary halides in THF in the presence of a catalyst formed in situ

from $FeCl_3$ and TMEDA as the preferred additive.[41] Again, the reaction can be performed on a multigram scale. Since optically active (*S*)-2-bromooctane is completely racemized when reacted with PhMgBr/[Fe], it was speculated that "iron bound radicals" might be passed through at some stage of the reaction pathway.



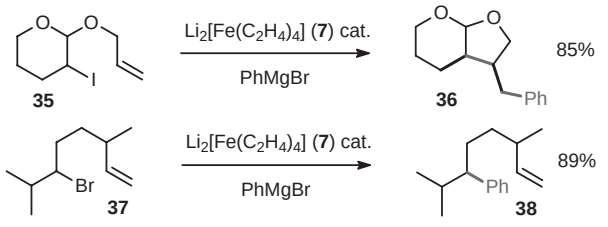
Scheme 12.

Similar studies by Nagano and Hayashi showed that TMEDA can be omitted if the catalyst is prepared from $Fe(acac)_3$ and aryl Grignard reagents in Et_2O.[42] These authors noticed an interesting chemoselectivity profile, which allows for a selective cross coupling of a primary alkyl bromide in the presence of an aryl triflate in Et_2O as the reaction medium (**32** → **33**); subsequent treatment of the resulting product with *n*-BuMgBr in THF/NMP engenders clean cross coupling of the remaining TfO group according to Fürstner's protocol (Scheme 12). More recently, Bedford et al. showed that [FeCl(salen)] complexes in Et_2O also afford very active catalysts for similar purposes.[43]



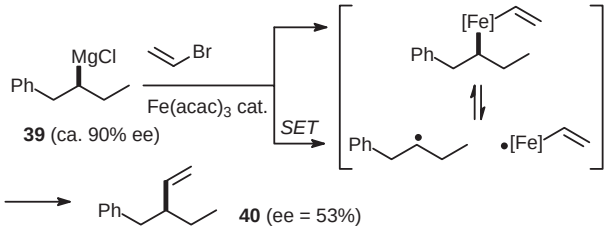
Scheme 13.

A comprehensive study on iron catalyzed cross couplings of alkyl halides was published by Fürstner and Martin.[22] In accordance with the proposal that low valent iron species might be decisive intermediates, the Fe(−II) ate complex $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ (**7**)[23] was found to be a superbly active and selective catalyst. It is remarkable that primary alkyl iodides as well as secondary bromides can be selectively cross coupled with ArMgX even in the presence of ketone, ester, isocyanide, chloride, nitrile, ether, acetal or amine groups in the substrates (Scheme 13).



Scheme 14.

Allylic and propargylic halides also react with high efficiency. A clear cut mechanistic picture, however, is still elusive, in particular with regard to the possible intervention of radical species. This ambiguity becomes evident from the comparison shown in Scheme 14. While substrate **35** undergoes a 5-*exo-trig* cyclization prior to cross coupling,[22,44,45] the closely related substrate **37** affords the "regular" product **38** in similar yield.[22] To account for these results, an investigation reported by Hoffmann et al. on the cross coupling of the chiral, enantio-enriched alkyl Grignard reagent **39** with vinyl bromide is instructive (Scheme 15).[46]

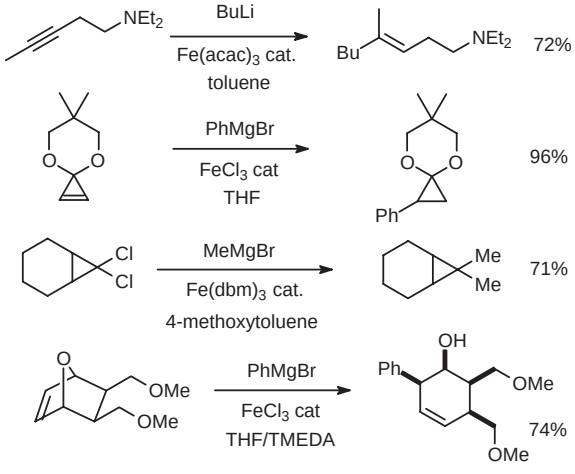


Scheme 15.

These authors assume the formation of a transient diorganoiron species that is prone to reversible homolysis. Alternatively, an SET event might furnish the radicals first which then combine to give the organometallic species en route to the product. Such a scenario accounts for the partial racemization observed in this particular experiment (**39** → **40**) and might also provide an explanation for the formation of products such as **36** which supposedly derive from radical intermediates.

♦ *Further Extensions*

A growing number of publications shows that iron catalysts effect yet other useful C–C-bond formations. Although a comprehensive coverage is beyond the scope of this account, a few remarkable examples are depicted in Scheme 16. Among them, carbometallations of alkynes[47] and strained alkenes,[48] the dimethylation of *gem*-dichlorocyclopropanes,[49] and the alkylative ring opening of oxabicycloheptenes[50] are particularly noteworthy. Finally, the established utility of iron-catalyzed ene reactions[51] and a report on selective 1,6-additions[52] deserve mentioning.



Scheme 16.

The low price, ready availability, and benign character of iron salts, combined with the exceptional reactivity and impressive functional group tolerance of the catalysts derived thereof result in an attractive application profile of iron-catalyzed C–C-bond formations. Recent successful implementations into various total syntheses and industrially relevant processes augur well for the future development of this fascinating area of research.

♦ Acknowledgement

Financial support by the DFG (Leibniz award to A. F.), the Fonds der Chemischen Industrie, and the Alexander-von-Humboldt Foundation (fellowship to R. M.) is gratefully acknowledged.

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