The Promise and Challenge of Iron-Catalyzed Cross Coupling

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RECEIVED ON FEBRUARY 4, 2008

CONSPECTUS

Transition metal catalysts, particularly those derived from the group VIII−X metals, display remarkable efficiency for the formation of carbon−carbon and carbon−heteroatom bonds through the reactions of suitable nucleophiles with organic electrophilic partners. Within this subset of the periodic table, palladium and nickel complexes offer the broadest utility, while additionally providing the deepest mechanistic insight into thus-termed "cross-coupling reactions". The mammoth effort devoted to palladium and nickel catalysts over the past 30 years has somewhat obscured reports of alternative metal complexes in this arena. As cross-coupling reactions have evolved into a critical support for modern synthetic chemistry, the search for alternative catalysts has been taken up with renewed vigor.

When the current generation of synthetic chemists reflects back to the origins of cross coupling for inspiration, the well-documented effect of iron salts on the reactivity of Grignard reagents with organic electrophiles surfaces as a fertile ground for alternative catalyst development. Iron possesses the practical benefits more befitting an alkali or alkaline earth metal, while displaying the unique reactivity of a d-block element. Therefore the search for broadly applicable iron catalysts for cross coupling is an increasingly important goal in modern synthetic organic chemistry.

This Account describes the evolution of iron-catalyzed cross coupling from its inception in the work of Kochi to the present. Specific emphasis is placed on reactivity and synthetic applications, with selected examples from acyl-, alkenyl-, aryl-, and alkyl halide/pseudohalide cross coupling included. The typical reaction partners are Grignard reagents, though organomanganese, -copper, and -zinc derivatives have also been used in certain cases. Such iron-catalyzed processes occur very rapidly even at low temperature and therefore are distinguished by broad functional group compatibility. Furthermore, recent advances in carbon−heteroatom bond formation and studies relevant to the general reactivity of in situ generated and structurally defined "low-valent" iron catalysts are presented.

The preparative aspects of iron-catalyzed cross coupling are encouraging, but the inclination to classify these processes within the characteristic reaction manifold is premature, as mechanistic studies have evolved at a comparatively slow pace. A typical protocol for cross coupling employs an Fe(+2) or Fe(+3) precatalyst, which is reduced in situ by the organometallic nucleophile. The nature of the resulting active component(s) is still best described, more than 30 years later, in Kochi's original terms as a "reduced form of soluble iron". Despite huge gaps in our current knowledge, three distinct mechanisms have been formulated, largely based on empirical evidence: a "canonical" cross-coupling process, a manifold wherein alkylation of an organoiron intermediate replaces transmetalation as a key step, and finally a proposal reliant on the formation of nucleophilic ate complexes. Conjecture and speculation abound, but precisely what constitutes the catalytic cycle in iron-catalyzed cross coupling remains an extremely challenging unanswered question.

Introduction

Modern cross-coupling chemistry originates from a series of concurrent contributions published in the early 1970s.[1,2] Often perceived as the genesis of the field are the independent disclosures from the groups of Corriu and Kumada on nickel-

catalyzed reactions of Grignard reagents with alkenyl and aryl halides, which were followed shortly by similar reports using palladium-based systems.[2] The impact of these initial discoveries can hardly be overestimated. In the intervening decades, this chemistry has been advanced to a mature state, fundamentally affecting the logic of chemical synthesis and providing robust and practical solutions even on the industrial scale.[1]

Seminal as these contributions may be, literature reports relevant to cross coupling existed even earlier. When viewed through a somewhat broader lens, the dramatic influence of trace metallic impurities, for example, on the formation and reactivity of Grignard reagents was already noted in the early 20th century.[3,4] Of a variety of transition metal salts examined, iron, cobalt, and nickel compounds were particularly effective at inducing homocoupling upon attempted insertion of magnesium into an aryl halide, ArX. Because minute quantities of these transition metals suffice, it was reasoned that ArX must have served as the terminal oxidant.[3,4] Such observations may have provided the blueprint for subsequent cross-coupling experiments, wherein stoichiometric Grignard formation precedes reaction with an organic electrophile to be deliberately chosen. This emerging concept was quickly reduced to practice in the iron-catalyzed reactions of organomagnesium halides with benzyl bromide (1945),[5] acetyl chloride (1953)[6] and, most notably, alkenyl bromides (1971).[7−9] Although these early examples indicated a considerable substrate scope, the further development of iron-based reactions lagged far behind the group X metal catalysts. Given the potential advantages of iron, the fact that interest in the field waned is perhaps indicative of challenges unique to an earlier transition metal. This latency period ended only in the mid-1990s when the interest in iron catalysis began to rise steeply, driven by the desire to develop cost-effective and benign alternatives to the then established palladium- and nickel-based systems. It is the intent of this Account to provide a personal perspective on the current status of iron-catalyzed cross coupling rather than a comprehensive overview.[10,11] As will become evident, the field is both promising and murky, because we still lack the theoretical underpinning almost completely. The accumulating empirical data, however, allow for hypotheses to be formulated, which, we believe, provide direction for future efforts that will hopefully lead to a better understanding and thereby set the basis for more advanced applications.
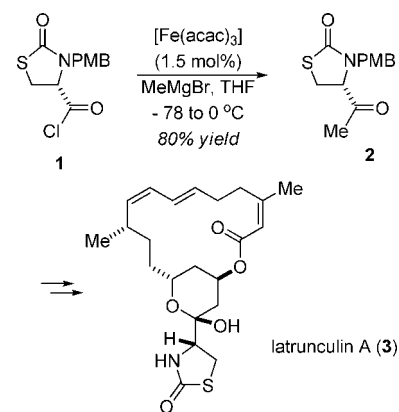
Preparative Aspects

Acid Chlorides. The selective monoaddition of nucleophiles to activated acid derivatives posed a significant challenge to

TABLE 1. Iron-Catalyzed Ketone Formation
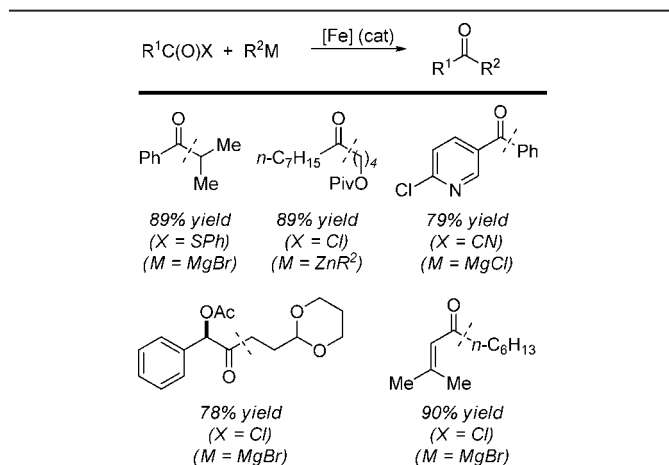
SCHEME 1. Iron-Catalyzed Acylation en Route to Latrunculin

the synthetic chemist in the first half of the 20th century. In attempts to remedy this deficiency, Cook and co-workers discovered that catalytic $FeCl_3$ was highly effective for controlling the addition of *n*-butylmagnesium chloride to acetyl chloride, affording 2-hexanone in >70% yield compared with 31% for the uncatalyzed process (eq 1).[6] It was only much
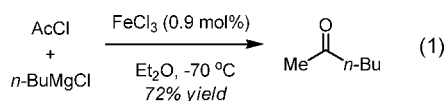
later that this transformation was generalized, allowing the coupling of a variety of functionalized acid chlorides, acid cyanides, and thioesters with primary, secondary, and tertiary alkyl and aryl Grignard reagents or diorganozinc derivatives in good to excellent yields under notably mild conditions.[12−14] In addition to the examples shown in Table 1, the preparation of ketone **2**, which served as a key building block for a concise total synthesis of the actin-binding macrolides of the latrunculin family, is representative (Scheme 1).[15] In this par-

SCHEME 2. Stereospecific Cross Coupling
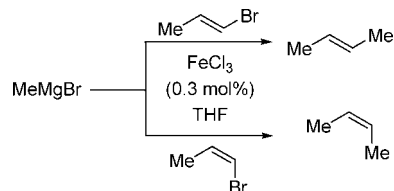
TABLE 2. Iron-Catalyzed Cross Coupling of Alkenyl Electrophiles
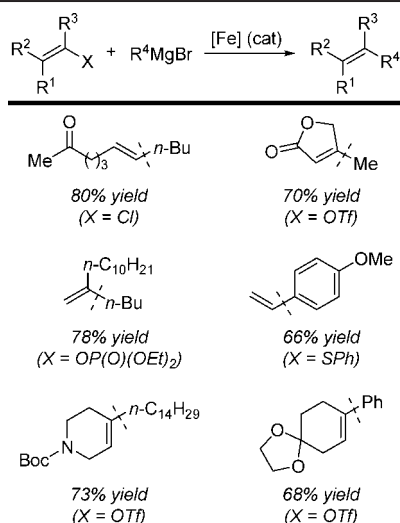
ticular case, the iron-catalyzed process proved far superior to the uncatalyzed and even to the copper-catalyzed addition reaction.

Alkenyl Electrophiles. The impact of cross coupling is most evident in the reaction of alkenyl and aryl electrophiles. In a contribution that predates nickel and palladium catalysis, Kochi et al. showed that alkenyl halides react with organomagnesium halides in the presence of catalytic amounts of $FeCl_3$.[7] They later found iron 1,3-diketonates to be superior precatalysts, because they are easier to handle and usually

result in higher overall yields.[8] Importantly, the stereospecificity of the reaction, generally considered a hallmark of cross-coupling technology, was clearly demonstrated (Scheme 2).[7]

A practical drawback of Kochi's original protocol was the requirement for ≥ 3 equiv of the alkenyl halide to reach full conversion of the Grignard reagent. By choice of the appropriate medium, however, it is possible to obtain high yields while employing nearly equimolar amounts of the reaction partners. This observation was first made by Molander for styrenyl halides where 1,2-dimethoxyethane was used as the solvent[16] and later generalized by Cahiez who noticed the beneficial effect of THF/*N*-methyl-pyrrolidinone (NMP) mixtures on the reaction outcome.[17]

In addition to alkenyl halides, related electrophiles such as alkenyl sulfones, sulfides, phosphates, and triflates are also suitable coupling partners (Table 2).[11,13,17,18] The iron-catalyzed bond formation usually outperforms the uncatalyzed addition of the Grignard reagent to other electrophilic sites in the substrate, thus rendering functional groups such as esters, ketones, enones, carbamates, or acetals compatible. Consequently, this methodology has been successfully implemented in target-oriented synthesis, among which the total synthesis of (−)-cubebene (**5**) and the late-stage application en route to ciguatoxin (**6 → 7**) are particularly striking (Scheme 3).[19,20]

In addition to the practical benefits associated with iron catalysts, chemical advantages over the better known noble metal systems have been documented in certain cases. One such instance is in the preparation of enantiopure bicyclic diene ligands where only the iron-based procedure provided (*R,R*)-**9** in high yield,[21] avoiding Grignard homocoupling, which plagues its nickel- and palladium-based relatives (Table 3).

SCHEME 3. Alkenyl Triflate Cross-Coupling Reactions in Total Synthesis
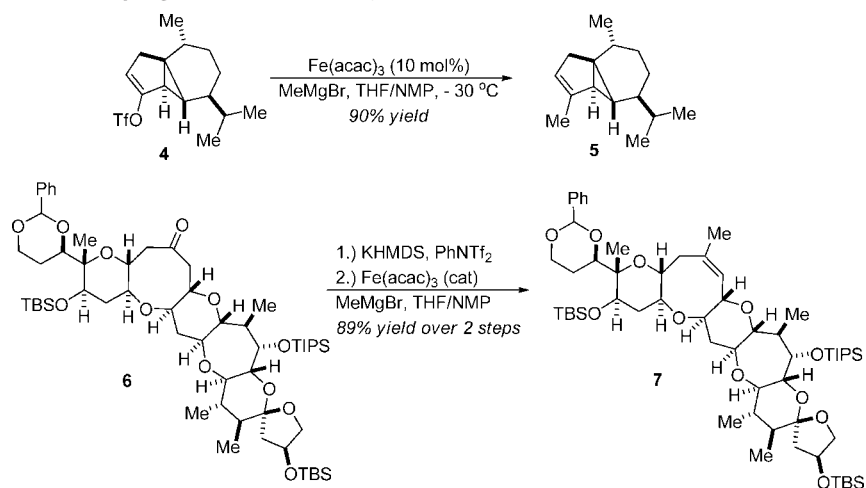
Although the majority of iron-catalyzed processes utilized Grignard reagents, other nucleophiles can be employed. Most notable are organomanganese chlorides, which rival their magnesium analogues in terms of yield and reactivity.[22,23]

Aryl Electrophiles. In 2002, our group reported iron-catalyzed cross-coupling reactions where aryl halides were the electrophilic partner.[24] In this study, a significant and unexpected reactivity trend was observed (Table 4). Whereas aryl iodides and bromides, preferred substrates for palladium- and nickel-catalyzed processes, led to substantial formation of the reduced product, the corresponding aryl chlorides, triflates, or tosylates resulted in a rapid and selective cross coupling on treatment with alkyl Grignard reagents in the presence of FeX_3 (X = Cl, acac).[24]

A wide variety of aryl and heteroaryl substrates take part in this process, though electron-rich arenes require the use of the more reactive triflates.[24,25] Likewise, the scope with respect to the nucleophilic partner is reasonably broad, as primary and secondary alkyl Grignard reagents function well, provided that [Fe(salen)Cl] is used as the precatalyst in the latter case.[24] Furthermore, alkyl zincates and organomanganese reagents were found appropriate, whereas organolithium species usually failed to deliver the desired products.[24] Interestingly, allyl, vinyl, and aryl Grignard reagents uniformly led to poor yields in reactions performed with FeX_3 (X = Cl, acac) in THF/NMP. However, it was later found that the use of arylcopper reagents[26] or of an FeF_3-based catalyst system[27] permits efficient aryl—aryl bond formation with electron-poor aryl iodides or aryl chlorides, respectively (see below).

$$(2)$$

7 min, 16 g scale
79 - 84% yield
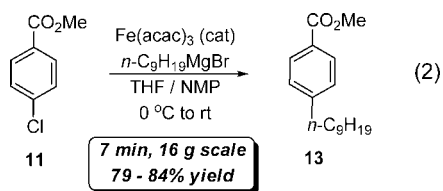
In addition to using an inexpensive, stable, and benign precatalyst, $Fe(acac)_3$-catalyzed alkyl—aryl cross-coupling processes are distinguished by exceptionally high reaction rates and are readily amenable to scale up. Instructive cases include the formation of an intermediate for the synthesis of the immunosuppressive agent FTY720,[28] as well as of 4-nonylbenzoate **13**, a valuable component of liquid-crystalline materials (eq 2).[29] Both compounds could be made in multigram quantities on the time scale of minutes at 0 °C. These mild conditions are also thought to be responsible for the observed chemoselectivity profile, as various functional groups, which are a priori susceptible to attack by the Grignard reagent, were found compatible (Table 5).[24–28] Note, however, that the reac-

TABLE 3. Comparison of Different Methods for the Formation of Diene **9**

entry	catalyst (mol %)	T (°C)	9/10	yield (%)
1	$NiCl_2(dppe)$ (1)	40	0.7	44
2	$PdCl_2(dppf)$ (1)	40	0.6	45
3	$Co(acac)_3$ (5)	0	0.6	28
4	$Fe(acac)_3$ (5)	0	13	98

TABLE 4. Effect of the Leaving Group

entry	X	yield, % (R = n-C_6H_{13})	yield, % (R = H)
1	I	27	46
2	Br	38	50
3	Cl	>95	
4	OTf	>95	
5	OTs	>95	

tion is sensitive to steric hindrance, as aryl chlorides bearing *ortho* substituents generally afford lower yields than their *para*-substituted counterparts. As an additional asset, (hetero)arenes with more than one halide or pseudohalide are amenable to either selective monosubstitution or sequential one-pot cross coupling.[13] These features are exemplified by largely catalysis-based syntheses of the spermidine alkaloid (−)-isooncinotine (**16**, Scheme 4)[30] and the olfactory macrocycle (+)-muscopyridine (**20**, Scheme 5),[31] respectively.

As mentioned earlier, the success of iron-catalyzed cross coupling did not immediately translate into an effective solution for aryl—aryl bond formation. These reactions remained plagued by homocoupling of the Grignard reagent and were essentially limited to electron-deficient haloarenes.[24,32] Recent reports, however, suggest that formation of a variety of biaryl frameworks can be realized by modification of the precatalyst composition. Notably, homocoupling of the Grignard reagent is effectively reduced when FeF_3 is employed in combination with an *N*-heterocyclic carbene ligand (Table 6).[27] The specific effect of fluoride was demonstrated by the addition of KF to an $FeCl_3$ catalyst precursor, which otherwise provides predominately homocoupling product (entry 4).

Alkyl Halides. Alkyl halides have historically been challenging substrates for transition metal catalyzed cross coupling due to the high barrier to oxidative addition and the proclivity of the once-formed metal—alkyl complexes toward β-hydride elimination. It took several rounds of careful opti-

TABLE 5. Examples of Iron-Catalyzed Aryl–Alkyl Cross Coupling

$$\text{ArX} \quad + \quad \text{RMgBr} \quad \xrightarrow{\text{[Fe] (cat)}} \quad \text{ArR}$$

72% yield
(X = Cl)

80% yield
(X = OTf)

68% yield
(X = Cl)

84% yield
(X = Cl)

89% yield
(X = Cl)

60% yield
(X = Cl)

58% yield (X = Cl)
76% yield (X = OTf)
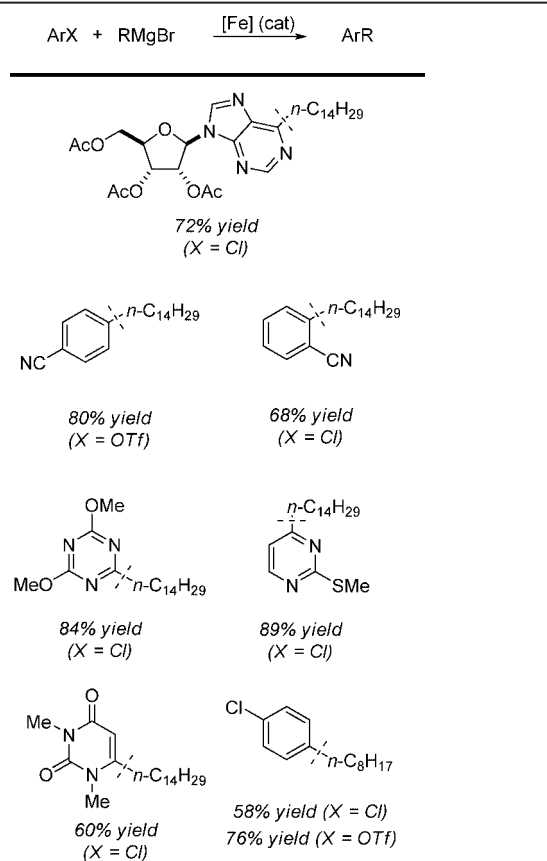
SCHEME 4. Selective Monosubstitution of a Dichloroarene

isooncinotine (16)
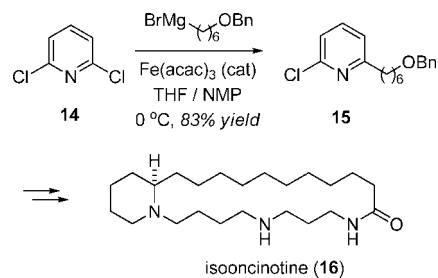
SCHEME 5. Iron-Catalyzed One-Pot Sequential Cross Coupling

muscopyridine (20)
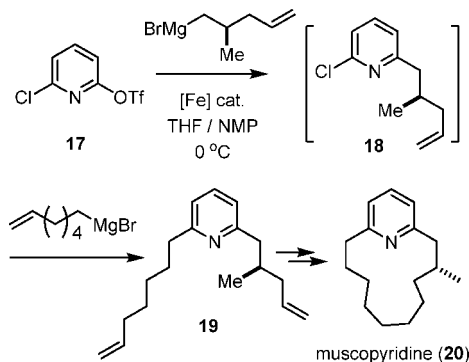
mization of the ligand sets until appropriate conditions were found to allow such substrates to undergo cross coupling with

**TABLE 6.** Fluoride Effect in Iron-Catalyzed Aryl–Aryl Cross Coupling

entry	FeX$_3$	L (mol%)	22/23/24 (%)
1	FeF$_3\cdot$3H$_2$O	SIPr$\cdot$HCl (15)	98:<1:4
2	FeF$_3\cdot$3H$_2$O		6:trace:4
3	FeCl$_3$	SIPr$\cdot$HCl (15)	32:2:32
4	FeCl$_3$	KF (20) SIPr$\cdot$HCl (15)	92:1:8

TABLE 7. Effect of Additives on Cross-Coupling Reactions of Alkyl Halides.

entry	additive	R = Ph (%)	R = H (%)	27 (%)
1	none	5	0	79
2	NMP	15	trace	3
3	TMEDA	71	3	19

the aid of palladium or nickel complexes.[33] Therefore it is surprising that relatively unsophisticated iron compounds proved competent for the cross coupling of a variety of primary and secondary alkyl halides.

Three distinct solutions were presented in 2004. Nakamura discovered a substantial influence of Lewis-basic additives on the reaction of cycloheptyl bromide with PhMgBr (Table 7).[34] In the absence of any additive, olefin **27** was the predominant product, and though the addition of NMP was to no avail, the use of tetramethylethylenediamine (tmeda) largely suppressed elimination. Upon slow addition of the Grignard reagent to the reaction mixture, the yield of **26** could be improved to 90% on an 8 g scale.[34]
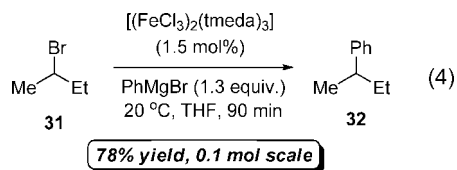
(3)
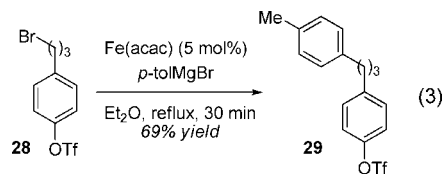
Immediately following the Nakamura report, Hayashi presented an alternative protocol devoid of any additive but requiring Et$_2$O as the solvent.[35] Remarkably, these conditions were found to be selective for an alkyl halide in the presence of an aryl triflate (eq 3); as the latter undergoes cross coupling with an alkyl Grignard reagent in THF/NMP, this partic-

ular example showcases the subtle differences in reactivity exhibited by catalysts generated in situ from the same precursor salt.

The only example of a structurally defined low-valent iron catalyst able to effect the cross coupling of alkyl halides was reported in the same year by our group.[36] Specifically, it was shown that the ferrate complex [Fe(C$_2$H$_4$)$_4$][Li(tmeda)]$_2$ (**30**) induces reactions of aromatic Grignard reagents with a variety of alkyl, allyl, and propargyl halides, even in the presence of esters, ketones, nitriles, isocyanates, or *tert*-amines (Table 8).[36] Complex **30** can be obtained on large scale as an air-sensitive crystalline material on treatment of ferrocene with lithium under an ethene atmosphere.[37] Because the central iron atom displays a formal oxidation state of −2 and is bound to four kinetically labile olefin ligands, it constitutes a highly nucleophilic and accessible reactive site.

Following these initial reports, several modified catalyst systems have been described that differ in the ligand sets of the iron precatalyst or try to fine-tune its activity by addition of proper Lewis-basic additives.[38] A particularly practical procedure uses the preformed complex [(FeCl$_3$)$_2$(tmeda)$_3$] and thereby avoids the need for ≥1 equiv of tmeda as had been required in Nakamura's original recipe.[39] This advantage is particularly manifest from the example shown in eq 4, which readily scaled to 0.1 mol of product and required no more than 1.5 mol % of the iron−tmeda adduct.

(4)

TABLE 8. Alkylations Catalyzed by the Low-Valent Ferrate Complex **30**

SCHEME 6. Iron-Catalyzed Carbometalations[a]

[a] Conditions: (a) Fe(acac)$_3$ (5 mol %), IPr (20 mol %), THF, 60 °C, 16 h, then H$_2$O, 91% yield; (b) FeCl$_3$ (3 mol %), THF, −78 to −25 °C, then sat. NH$_4$Cl, 96% yield; (c) Fe(acac)$_3$ (2 mol %), PhMe, −78 °C, 88% yield.

More recently, the iron-catalyzed cross coupling of alkyl halides was extended to alkenyl and even alkyl Grignard reagents as the nucleophiles.[40,41] An alternative concept employs sulfonyl chlorides as the electrophiles, which are subject to desulfinylative C−C bond formation when exposed to Grignard reagents in the presence of Fe(acac)$_3$ (5 mol %).[42]
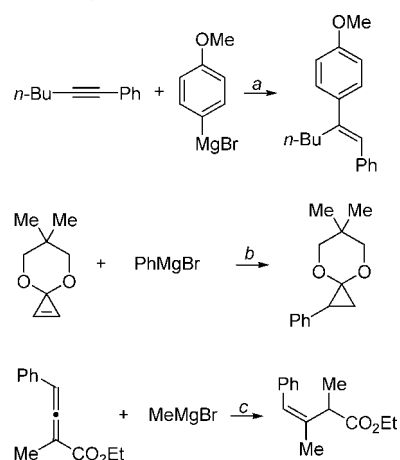
Although the mechanism of iron-catalyzed alkyl−aryl cross coupling remains largely unknown, evidence has accumulated that radical intermediates may play a role, at least in certain cases.[34,36,38] Whether this is general, however, and at which stage of the reaction coordinate the radicals possibly intervene remains to be elucidated.

Related Iron−Catalyzed C−C Bond Formations. Although not cross coupling in the strictest sense, the examples shown in Scheme 6 demonstrate that low-valent iron generated by procedures analogous to those outlined above

is capable of inducing a variety of other preparatively useful C−C bond formations. Particularly relevant in the present context are the *syn*-carbometalation reactions of alkynes,[43] strained cycloalkenes,[44] or electron-deficient olefins,[45] which supposedly generate transient alkenyl or alkyl iron intermediates similar to those obtained by direct oxidative insertion into organic halides.[46] These reactive intermediates, after transmetalation to magnesium, can be quenched with different electrophiles. In an alternative format, the presence of a propargylic leaving group in the substrate allows allenes to be accessed in a regio- and stereoselective manner. This concept was particularly successful with propargyl epoxides[47] and has already met the rigors of natural product total synthesis (Scheme 7).[48]

SCHEME 7. Total Synthesis of Amphidinolide Y
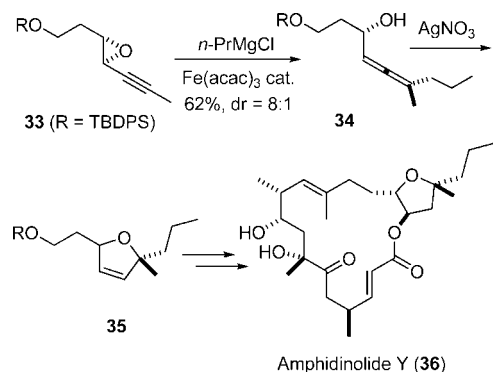
**SCHEME 8.** Cycloisomerization Reactions Catalyzed by a Low-Valent Ferrate Complex
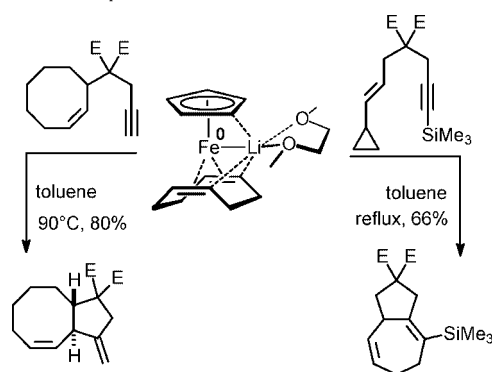
The reducing capability of low-valent iron is further demonstrated by cycloisomerization reactions of the Alder-ene or [5 + 2]-type, as well as by higher order cycloadditions, all of which are likely triggered by oxidative cyclization of suitable unsaturated substrates (Scheme 8).[49] Examples are known for both in situ generated catalysts and structurally defined ferrate complexes, which corroborates the supposedly close relationship between these different forms of low-valent iron.[49]

Iron-Catalyzed C−O, C−S, and C−N Cross Coupling. Very recent reports show that certain iron salt/ligand combinations can effect C−N, C−O, and C−S-bond formation. Specifically, a cooperative catalyst system comprising Fe-(acac)$_3$/CuO allows N-arylations of aromatic heterocycles or lactams to be carried out, whereas each reagent alone was unable to effect this transformation.[50] Shortly thereafter it was demonstrated that the use of *N,N'*-dimethylethylenediamine (dmeda) as an additive to FeCl$_3$ or Fe$_2$O$_3$ permits related N-arylations in the absence of added copper (Table 9).[51,52]

Although a direct translation of this protocol to C−O bond construction was unsuccessful, it was found that FeCl$_3$ in combination with 2,2,6,6-tetramethyl-3,5-heptanedione leads to an active catalyst system for diarylether formation.[53] The cross coupling of a variety of phenols with iodoarenes generally occurred in good yields and was found compatible with dif-

TABLE 9. Examples of Carbon−Heteroatom Bond Formations
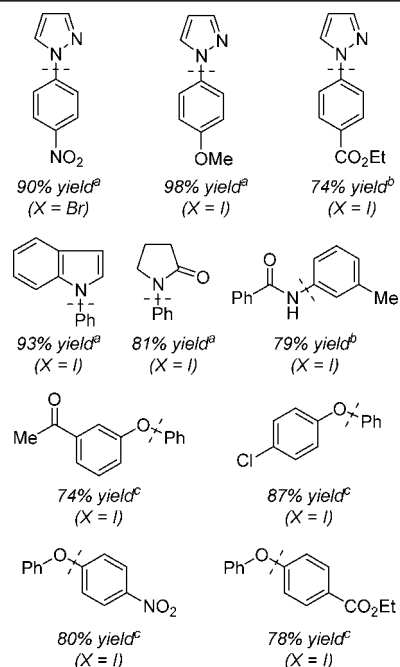
^{a} Conditions: CuO (10 mol %), Fe(acac)$_3$ (30 mol %), Cs$_2$CO$_3$ (2 equiv), DMF, 90 °C, 30 h. ^{b} Conditions: FeCl$_3$ (10 mol %), dmeda (20 mol %), K$_3$PO$_4$, PhMe, 135 °C, 24 h. ^{c} Conditions: FeCl$_3$ (10 mol %), (*t*-BuCO)$_2$CH$_2$ (20 mol %), Cs$_2$CO$_3$, DMF, 135 °C.

ferent functional groups in both partners (Table 9). Even though fairly high reaction temperatures are required, these reports constitute an interesting step toward benign alternatives for C−X bond formation.

Mechanistic Aspects

Canonical Cross Coupling. In his initial contribution, Kochi speculated that a "reduced form of soluble iron" serves as the active catalyst generated in situ from FeCl$_3$ and a Grignard reagent.[7] The proposed catalytic cycle evolved over several years to what is now perceived as the canonical mechanism for transition metal catalyzed cross coupling,[54] comprising a sequence of oxidative addition, transmetalation, and final reductive elimination steps (Scheme 9). Consistent with this hypothesis is the stereospecific course of the cross coupling of alkenyl halides (Scheme 2).[7] Although Fe(+1) was depicted as the active species in the original paper, the equivalent process involving Fe(0) was considered equally feasible.[7]

The active component is metastable and, when allowed to stand in the absence of substrate, rapidly loses catalytic competence. This propensity together with an exceptional sensitivity toward air and moisture rendered full characterization exceedingly difficult. Although electon paramagnetic resonance (EPR) active compounds were observed in the mixture, the oxidation state of the operating component remains

SCHEME 9. Kochi's Original Mechanistic Proposal
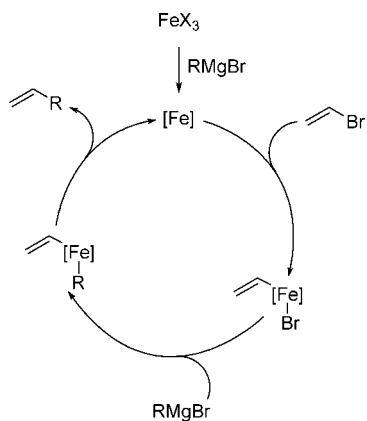
SCHEME 10. Putative Mechanism Based on a Low-Valent Intermetallic Catalyst
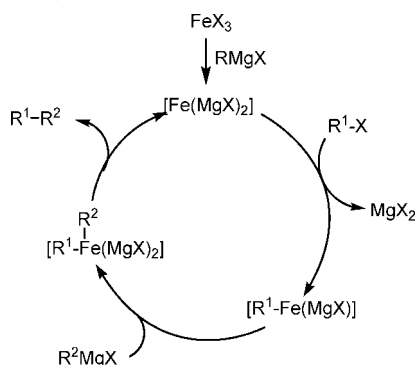
ambiguous.[7] Complementary spectroscopies have not yet been applied to this problem.

A Conceptually Different Mechanism Based on a Hetero-bimetallic Catalyst. It was not until 30 years later that Bogdanović and co-workers reinvestigated the stoichiometric reaction of $FeCl_2$ with alkyl-Grignard reagents.[55,56] Their data suggest that an overall four-electron reduction takes place, ultimately leading to an intermetallic species of the formal constitution $[Fe(MgCl)_2]_n$, which likely consists of small clusters incorporating magnesium and iron centers that are connected via fairly covalent intermetallic bonds.[55,56] Because the conditions of these experiments closely mimic those of standard cross-coupling protocols, a catalytic cycle initiated by such low-valent and supposedly highly nucleophilic entities was envisioned (Scheme 10).[24]

This proposal differs from Kochi's original mechanism in three distinct aspects:

(1) A *formal* Fe(−2)/Fe(0) rather than an Fe(+1)/Fe(+3) redox couple is presumed to be operative.

(2) In a formal sense, the reaction of $[Fe(MgCl)_2]_n$ with the organic halide constitutes a σ-bond metathesis rather than a conventional oxidative insertion; however, this is not
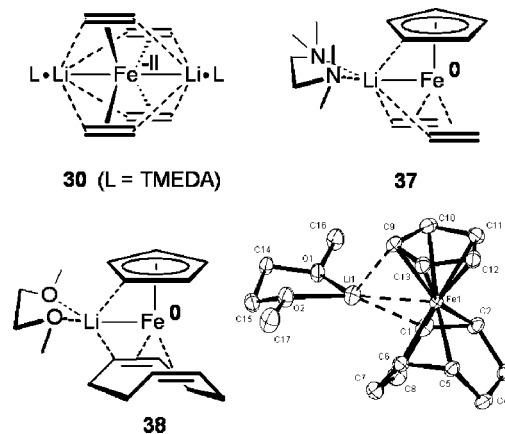

FIGURE 1. Examples of structurally defined low-valent ferrate complexes

meant to imply any mechanistic detail because different elementary steps can be conceived.

(3) Because no organoiron halide species is generated, the subsequent reaction with RMgX must occur by alkylation of the intermediate primarily formed rather than by transmetalation. The resulting diorganoiron species then undergoes reductive elimination to afford the product and regenerate the catalyst (Scheme 10).

Although this mechanism is largely a formalism at this stage, certain empirical evidence supports the basic aspects of this cycle.[24] Whereas highly activated Fe(0) powder is not catalytically competent, reaction with excess RMgX leads to a dark brown homogeneous solution that readily effects standard cross coupling. Because reducing conditions are maintained throughout, this experiment corroborates the view that the active iron species must have a formal oxidation state ≤ 0 and might eventually be ligated with organic residues derived from the nucleophilic partner.[24]

Furthermore, the reactivity of the in situ catalyst can be emulated with structurally well defined ferrate complexes such as **30**, **37**, or **38** (Figure 1).[37,57] Their iron centers exhibit *formal* oxidation states of −2 or 0 and feature fairly covalent bonds to the escorting lithium atoms. Because the kinetically labile ethylene ligands ensure a rather "bare" character of the central metal, such complexes show all structural characteristics one might expect for $[Fe(MgCl)_2]_n$. Prototype cross-coupling experiments confirm that **30**, **37**, and **38** are fully functional surrogates, their activity being comparable to or even higher than that of species generated by reduction of FeX_3.[36,57] Moreover, they were shown to undergo two-electron oxidations when exposed to chlorobenzene or allyl halides.[57] Therefore we are currently employing these com-

SCHEME 11. Oxidative Addition and Ligand Redistribution Processes

SCHEME 12. Strikingly Different Behavior of Methyl and Higher Alkyl Donors
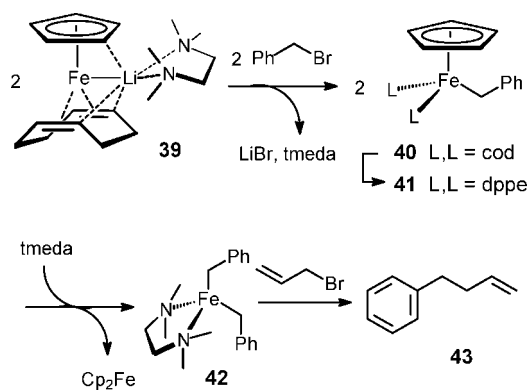
plexes to investigate the elementary steps supposed to account for iron-catalyzed bond formations in greater detail.[49,57]

Additional information comes from investigations by Sen et al. who convincingly showed that the oxidative insertion of **39** into benzyl halides occurs via two consecutive single-electron transfer steps.[58] The resulting complex **40** could be trapped with 1,2-bis(diphenylphosphino)ethane (dppe); however, in the absence of the phosphine, tmeda effects a ligand redistribution with formation of **42** as the major product. This species is capable of alkylating allyl bromide to afford the cross-coupling product **43** (Scheme 11).[58] These stoichiometric observations of Sen may be a useful entry point into examinations of the essential role tmeda plays in some of the iron-based protocols presently available. It is important to note, however, that these experiments were carried out in the absence of Grignard reagent and their relevance to the actual catalytic processes therefore remains to be seen.

Organoferrate Manifold. Based on the observation that a 1:1 mixture of alkene and alkane is formed from the Grignard reagent in the reduction of FeX_2, Bogdanović proposed a β-hydride elimination followed by a reductive elimination as two of the elementary steps in the formation of $[Fe(MgX)_2]$.[55,56] Extension of this concept to MeMgX is not possible because it lacks a β-hydrogen elimination pathway. This fundamental difference is consistent with our observations that different methyl donors failed to alkylate 4-chlorobenzoate **11** in the presence of catalytic Fe(acac)$_3$, even though this particular substrate reacts with ethyl or higher alkyl Grignard reagents with exceptional ease (Scheme 12).[13,24] However, since a number of successful reactions of MeMgX (and related nucleophiles) with more activated substrates such as alkenyl halides and triflates, electron-deficient heteroaryl halides, or acid chlorides have been reported,[7,11,13] it seems possible that iron-catalyzed C—C bond formations
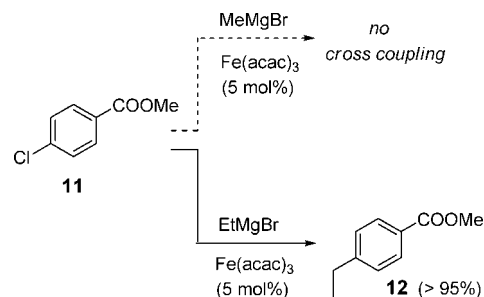
may occur in yet another reaction manifold. Therefore, attempts were made to characterize the reactive intermediates formed on treatment of iron salts with methyl donors.

Treatment of FeCl$_3$ with MeLi at low temperature results in a spontaneous reduction followed by an exhaustive alkylation of the resulting Fe(2+) center. As has been shown crystallographically, the resulting homoleptic complex incorporates an additional equivalent of MeLi to give the "super ate" complex [(Me$_4$Fe)(MeLi)][Li(OEt$_2$)]$_2$ (**44**) depicted in Figure 2.[57,59] Complex **44** mirrors the behavior of the in situ generated catalyst system very closely, because it fails to react with 4-chlorobenzoate but transfers methyl groups to more activated electrophiles. In addition, **44** acts as a base and as a single-electron transfer agent, suggesting that the chemoselectivity of organoferrate complexes in general may be more limited than previously assumed.[60] Overall, the reactivity profile of **44** has similarities to that observed with other ate complexes, most notably those of the copper series, and is clearly different from the behavior of higher alkyl Grignard reagents in the presence of FeX$_n$ (n = 2, 3).[60] To what extent related organoferrate species are formed with other donors incapable of undergoing the Bogdanović activation pathway by β-hydride
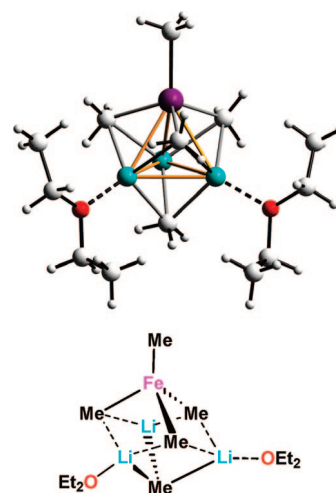
FIGURE 2. Structure of the iron "super ate" complex [(Me$_4$Fe)(MeLi)][Li(OEt$_2$)]$_2$ (**44**) in the solid state.

elimination remains to be elucidated. Our empirical observation, however, that phenyl-, alkenyl-, and allylmagnesium halides either fail or react only poorly with chlorobenzoate in the absence of special additives is suggestive. In fact, a homoleptic ate complex of the phenyl series of the composition [Ph$_4$Fe][Li(Et$_2$O)$_2$][Li(1,4-dioxane)] could recently be isolated in pure form.[57]

Assessment and Conclusions

Originally thought to be essentially limited to the reaction of alkenyl halides with unfunctionalized Grignard reagents, the field of iron-catalyzed cross coupling has entered a phase of significant growth. Substantial advancements have been made to increase the range of nucleophilic and electrophilic partners amenable to such transformations. Important examples include aryl chlorides and sulfonates, various acid derivatives, and even alkyl halides; the spectrum of nucleophiles now encompasses manganese-, zinc-, and copper-based donors to complement the organomagnesium halides commonly used. The ability to prepare highly functionalized Grignard reagents has further increased the scope of this methodology.[61]

The foregoing notwithstanding, iron-catalyzed cross coupling is not nearly as mature as its palladium and nickel counterparts. In particular, our insight into the reaction mechanisms is in its infancy, remains largely based on empirical evidence, and has yet to meet with similarly intense scrutiny as has been dedicated to the understanding of noble metal catalyzed transformations. Nevertheless, it is becoming increasingly clear that iron-catalyzed C−C bond formations fall into more than one distinct mechanistic category, with the organoferrate regime and the "low-valent" redox chemistry being limiting cases.[57] How and whether these manifolds are connected and what role additives may play in this regard remains essentially unknown.

To sustain advancement in this important area, however, the development of a firm conceptual framework by which the emerging empirical discoveries can be understood at the molecular level is of vital importance. Yet, we anticipate that any such endeavor constitutes a *tremendous* challenge. Not only are we lacking much of the fundamental knowledge about structure, electronics, and reactivity of nonstabilized "low-valent" iron compounds,[57,62] but any investigation into the actual in situ catalyst system must contend with highly reactive and potentially paramagnetic intermediates in a reaction mixture wherein more than one active species of poorly defined composition may be present.[57] The accessibility of a range of potential oxidation and spin states, readily traversed by one- or two-electron transfer steps and effected by subtle changes in the ligand environment, is a further complicating factor. Despite these daunting issues, the obvious practical relevance and potential economic benefits of using a cheap, readily available, nontoxic, and benign metal for bond-forming reactions as fundamental and widespread as cross coupling should suffice to drive research into all aspects of the chemistry of low-valent iron.

BIOGRAPHICAL INFORMATION

Benjamin D. Sherry received a B.S. degree in chemistry from Case Western Reserve University in 2002. He carried out doctoral research under the supervision of Professor F. Dean Toste at the University of California, Berkeley, and obtained his Ph.D. in 2007. He is currently a postdoctoral fellow in the laboratory of Professor Fürstner at the Max-Planck-Institut für Kohlenforschung, Mülheim, Germany.

Alois Fürstner obtained his Ph.D. in 1987 at the Technical University Graz, Austria. After a postdoctoral stay with the late Prof. Oppolzer in Geneva, Switzerland, and completion of his Habilitation, he joined the Max-Planck-Institut für Kohlenforschung, Germany (1993), where he was promoted to the rank of Director in 1998. His research program tries to engage the methodological and the application sides of organometallic catalysis into a fertile crosstalk.

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