METAL-CATALYZED CROSS-COUPLING REACTIONS: ENTERING THE IRON AGE
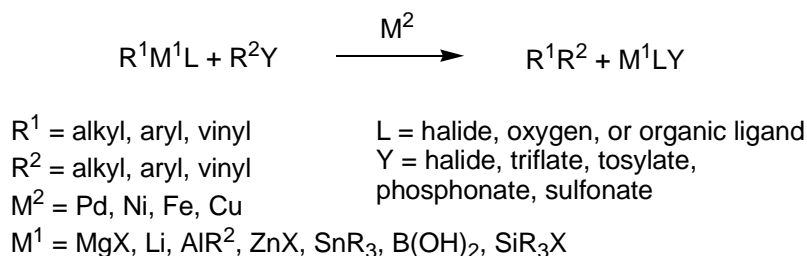
Reported by Christina Thompson   October 7, 2004

INTRODUCTION

The central importance of carbon-carbon bond forming reactions in organic synthesis has lead to intense investigation of cross-coupling reactions over the last thirty years.[1] Many transition metals are effective promoters and catalysts for cross-coupling reactions, including copper, palladium, nickel and iron (Scheme 1). Palladium and nickel are the most broadly employed and powerful catalysts for cross-coupling reactions.[2] Although iron-catalyzed cross-coupling reactions were first described within a year of the initial reports using palladium and nickel,[3] they were for the most part overlooked for thirty years while palladium and nickel were developed. Recently, attention has returned to the use of iron for cross-coupling reactions between Grignard reagents and a host of aryl and alkyl halides, triflates,[4] tosylates,[5] and phosphates.[6]

Scheme 1. Metal-catalyzed cross-coupling reaction with transition metal.

$$R^1M^1L + R^2Y \xrightarrow{M^2} R^1R^2 + M^1LY$$

R^1 = alkyl, aryl, vinyl   L = halide, oxygen, or organic ligand
R^2 = alkyl, aryl, vinyl   Y = halide, triflate, tosylate,
M^2 = Pd, Ni, Fe, Cu   phosphonate, sulfonate
M^1 = MgX, Li, AlR^2, ZnX, SnR$_3$, B(OH)$_2$, SiR$_3$X

The substrate scope of iron-catalyzed cross-coupling reactions is complimentary to that of palladium and nickel in that iron is capable of catalyzing the reaction of a broad range of chlorides, as well as a broad range of alkyl halides with organometalic donors, an area in which palladium is currently limited. This complimentary nature can be rationalized from the mechanism, in which the catalytic iron species is in a negative two oxidation state. This review introduces transition metal-catalyzed cross-coupling reactions, discusses palladium-catalyzed cross-coupling reactions as the current state-of-the-art, and then discusses the substrate scope of iron-catalyzed cross-coupling reactions. The postulated mechanism of iron-catalyzed cross-coupling reactions is then discussed.

BACKGROUND

Palladium is arguably the most extensively employed and thoroughly investigated of all the

transition metals for cross-coupling reactions.[7] The rate, yield, and scope of palladium-catalyzed cross-coupling reactions are influenced by both the reaction partners and the choice of ligands, allowing for a wide substrate scope through judicious choice of these parameters. Historically, palladium catalyzed cross-coupling reactions used iodides and bromides as the organic acceptors, however, alkyl phosphine ligands, as well as N-heterocyclic carbenes have recently been developed[8,9] that extend the substrate scope of palladium-catalyzed cross-coupling reactions to include aryl chlorides. Although these ligands are generally expensive, and the rates are still not as good as palladium-catalyzed cross-coupling reactions with bromides and iodides, the low cost, greater availability, and greater stability of chlorides makes this an important advance in the use of palladium-catalyzed cross-coupling reactions. The organometallic donors in palladium-catalyzed reactions can be a variety of metals, including tin, zinc, aluminum, boron, or silicon. Although Grignard reagents are very reactive and readily available, they are infrequently used in palladium-catalyzed reactions due to functional group incompatibilities.[10]

Nickel has also been used extensively as a catalyst in cross-coupling reactions. Acyl chlorides can be successfully coupled with Grignard reagents in nickel-catalyzed reactions, [11] which give it an advantage over palladium. At the same time, nickel catalysts have some significant and well documented disadvantages, including low selectivity,[12] low tolerance of functional groups,[13] and high toxicity.[14] For example, nickel-catalyzed cross-coupling reactions are known to rearrange *sec*-alkyl Grignard reagents, to produce significant amounts of the *n*-alkyl Grignard coupling product.[15]

SUBSTRATE SCOPE OF IRON-CATALYZED CROSS-COUPLING REACTIONS

Iron-catalyzed cross-coupling reactions proceed most efficiently with chloride substrates, which is in contrast to the aryl iodides or bromides usually required for palladium cross-coupling reactions.

Scheme 2. Comparison of aromatic halides in iron-catalyzed cross-coupling reactions

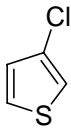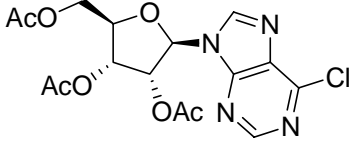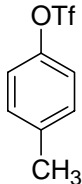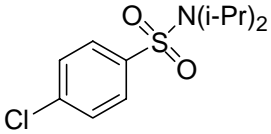|	**2**	**3**
X = Br	27%	46%
X = I	38%	50%
X = Cl	95%	-
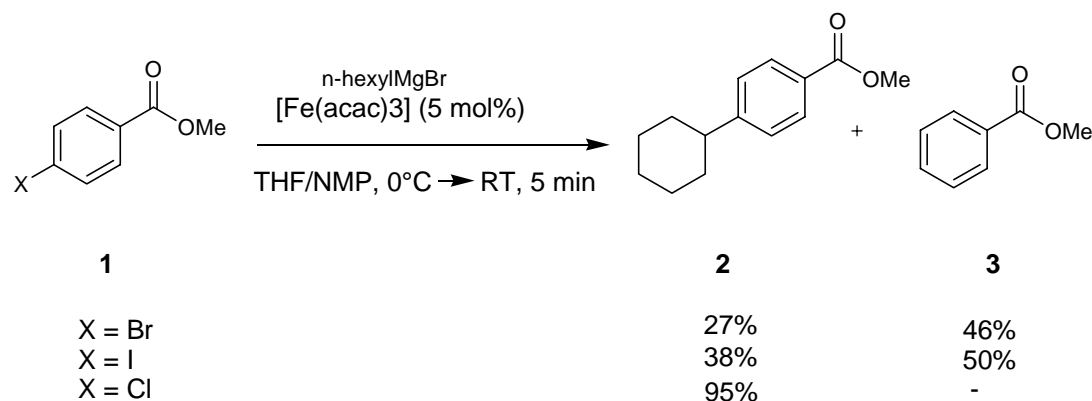
Fürstner studied the relative rates of iron-catalyzed cross-coupling reactions of aromatic iodides, bromides and chlorides and found that the aryl chloride is the most reactive substrate and produces the least amount of reduced byproduct **3**[16] (Scheme 2). With methyl 4-iodo- and 4-bromobenzoate, *n*-hexylmagnesium halides give 50 and 46% yields of

the reduced product **3** and only 27 and 38% of the desired product, respectively. On the other hand, methyl-4-chlorobenzoate reacts in virtually quantitative yield in only a few minutes to yield the coupled product **2**. Triflates and tosylates react similarly affording **2** in >95% yield.

Table 1. Selected examples of alkyl-aryl cross-coupling reactions[a]

aromatic electrophile	alkyl Grignard reagent	yield %
3-chlorothiophene structure	n-$C_{14}H_{29}MgBr$	41
nucleoside structure (AcO, OAc, OAc, Cl-purine)	n-$C_{14}H_{29}MgBr$	72
4-methylphenyl triflate (OTf, CH$_3$)	n-$C_{14}H_{29}MgBr$	81
4-chlorophenyl sulfonamide (O$_2$S-N(i-Pr)$_2$, Cl)	n-$C_6H_{13}MgBr$	94

[a]For reaction conditions, see ref. 1

Interestingly, Grignard reagents undergo cross-coupling faster than they react with other electrophilic sites in the substrate. For example, ketones, aldehydes, esters, ethers, nitriles, and even trimethylsilyl groups in the electrophilic halide partner are all compatible with Grignard reagents in the presence of iron.[17] The compatibility of the Grignard reagents with organic functionality is very important for the synthetic utility of iron-catalyzed cross-coupling reactions.

The success of iron-catalyzed cross-coupling reactions between aryl halides and aryl Grignard reagents are very dependent to the electronic nature of the aryl halide. In contrast, iron-catalyzed cross-coupling reactions between alkylmagnesium halides and aromatic electrophiles encompasses a diverse substrate scope. A variety of aryl chlorides, triflates, and tosylates react in good to excellent yields (Table 1).

Acid chlorides react with Grignard reagents under iron-catalysis in a very general synthesis of aromatic and aliphatic ketones. These couplings are characterized by short reaction times, few side reactions, and high yields. Interestingly, the rate of the catalyzed acylation reaction is faster than that of the cross-coupling reaction, thus allowing halides and other electrophilic substituents to be present in the substrates.[18]

One of the main advantages of iron catalysis is the ability to couple alkyl halides with aryl Grignard reagents, as this is an area which is still limited for palladium catalysis. Nakamura and co-workers have shown that iron catalysts are capable of inserting into both primary and secondary sp[3]-

hybridized carbon-halide bonds to affect cross-coupling (Scheme 3).[15] The ability to utilize sp³-hybridized carbon-halides represents a significant advance in cross-coupling reactions.

Iron-catalyzed cross-coupling reactions show remarkable solvent dependence. Adding *N*-methyl-pyrrolidinone (NMP) as a co-solvent suppresses the formation of side products formed through halogen-hydrogen reduction.[19] The presence of NMP as a co-solvent also allows alkenyl halides to react readily with a variety of aryl and alkyl Grignard reagents to afford highly substituted olefins with retention of configuration and drastically

Scheme 3. Alkyl-aryl iron-catalyzed cross-coupling reactions

improved yields (Scheme 4).[20] The polar nature of NMP is believed to help stabilize the iron
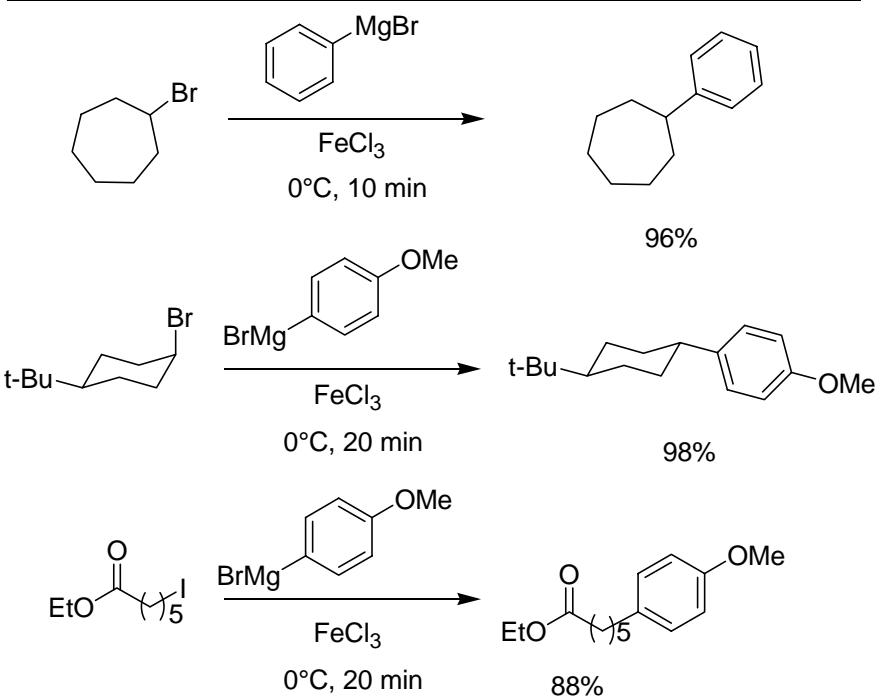
Scheme 4. Reaction of alkenyl halides with Grignard reagents with NMP
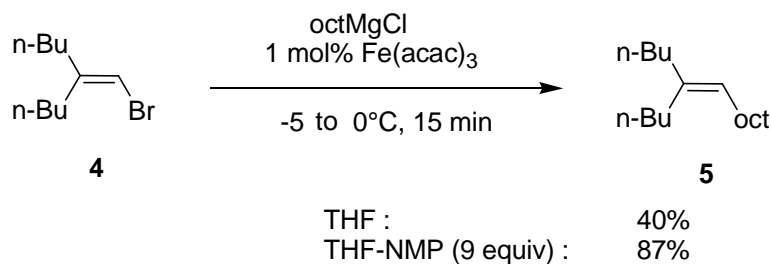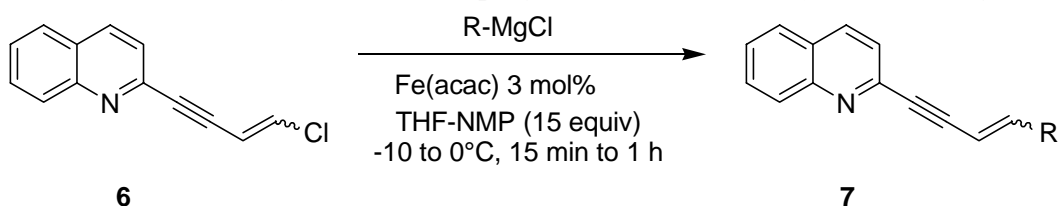

organometallic species in the catalytically active species.[19] Interestingly, in the case of alkyl-aryl cross-coupling reactions, it was found that NMP does not have any affect on the reaction, but that the addition of TMEDA suppresses the elimination side reaction.[21] In the case of aryl-aryl cross-coupling, where halogen-hydrogen reduction does not occur, the best yields are obtained when these reactions are carried out in THF rather than NMP.[22]

Iron salts are less toxic than palladium and nickel salts.[10] This advantage was exploited by Seck, *et al.* in their synthesis of 2-substituted quinolines, which are interesting targets because of their known leishmanicide properties.[23] Whereas palladium, nickel, manganese, and iron are all effective cross-coupling catalysts for the chloroenynes used in this synthesis, iron was chosen so that the library could be tested directly after purification, without the need for additional palladium or nickel scavengers (Scheme 5).

Scheme 5. Iron-catalyzed cross-coulping reaction of chloroenynes with Grignard reagents

$$ 6 \xrightarrow[\substack{\text{Fe(acac) 3 mol\%} \\ \text{THF-NMP (15 equiv)} \\ \text{-10 to 0°C, 15 min to 1 h}}]{\text{R-MgCl}} 7 $$

MECHANISM OF CROSS-COUPLING REACTIONS OF GRIGNARD REAGENTS DEVOID OF β-HYDROGENS

$$ FeCl_2 + 4\ MeMgBr \longrightarrow Me_4Fe^{II}(MgBr)_2 + 2\ MgBr_2 $$
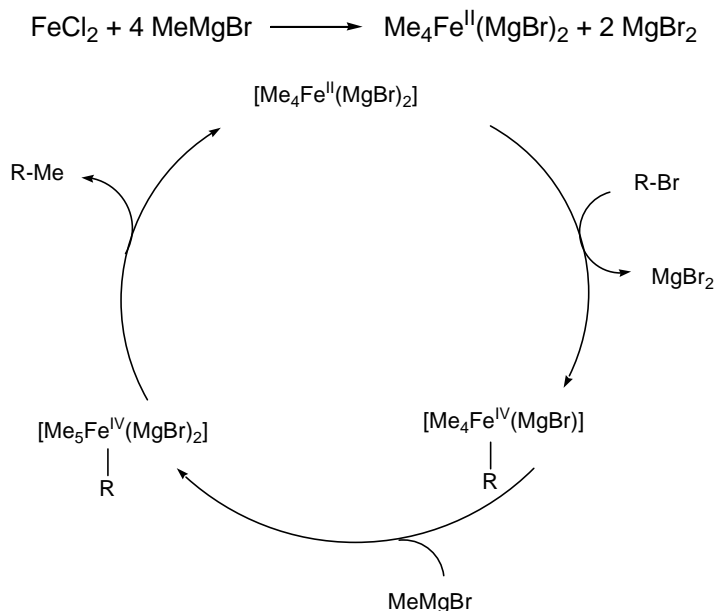
Figure 1. Postulated catalytic cycle for cross-coulping alkyl bromines with the system [MeMgBr + 5 mol% FeCl$_3$]

The mechanism of iron-catalyzed cross-coupling reactions of organometallic donors that do not contain β-hydrogens is similar to that of palladium and nickel-catalyzed cross-coupling reactions, as illustrated by the catalytic cycle of methylation of an aryl halide. Iron (III) chloride enters the cycle by first being reduced to Fe(II)Cl$_2$ in situ by one equivalent of MeMgBr.[24] The resulting Fe(II) precursor then reacts with four equivalents of Grignard reagent in an isohyptic ligand exchange reaction. This Fe(II) species undergoes oxidative addition with the organic acceptor to yield an Fe(IV) species. Despite the presence of four methyl groups on the iron, it is proposed that this complex reacts with a Grignard reagent to promote reductive elimination which provides the methylated aryl halide, and regenerate the catalytic Fe(II) complex (Figure 1).

MECHANISM FOR CROSS-COUPLING REACTION OF GRIGNARD REAGENTS CONTAINING β-HYDROGENS

One of the major challenges for the cross-coupling reactions with organometallic reagents that contain β-hydrogens is the problem of β-elimination. This process has a major impact on the catalytic cycle of iron-catalyzed cross-coupling reactions. Fürstner and co-workers propose that the catalytically active iron complex in reactions with Grignard reagents that contain β-hydrogens has a formal oxidation state of negative two. Negative oxidation states of iron have precedence in the literature, including

Collman's work on the highly nucleophilic Fe(-II) compound Na$_2$Fe(CO)$_4$.[25] Bogdanovic and co-workers have established

Scheme 6. The reaction of FeCl$_2$ with four equivalents of Grignard reagent

$$Fe^{II}Cl_2 + 4\ RCH_2CH_2MgX \longrightarrow [Fe^{-II}(MgX)_2] + 2MgX_2$$

that FeCl$_2$ is reduced in situ by four equivalents of Grignard reagent to form an iron(-II) complex of formal composition [Fe(MgX)$_2$][26] (Scheme 6).

Fürstner proposes that this reduced form of iron then enters the catalytic cycle as Fe(-II). Subsequent oxidative addition of the iron complex to the organic acceptor gives an Fe(0) complex. This complex then undergoes transmetallation with the organomagnesium reaction partner. This event is isohypsic, and yields an iron complex that now has two organic grou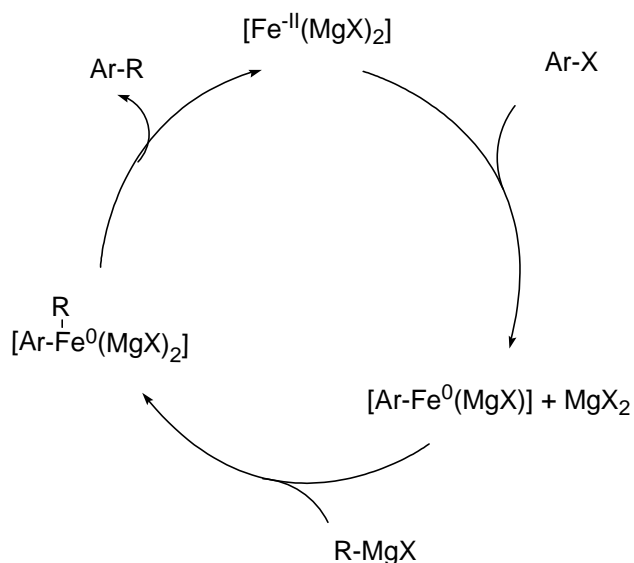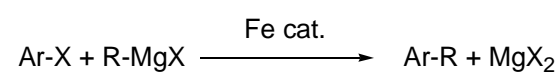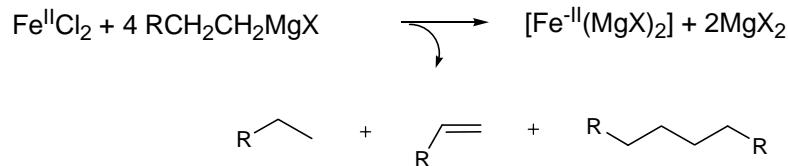ps attached to it. Reductive elimination then takes place, forming a new carbon-carbon bond, and regenerating the Fe(-II) catalytic species (Figure 2).[1]

$$Ar\text{-}X + R\text{-}MgX \xrightarrow{\text{Fe cat.}} Ar\text{-}R + MgX_2$$

Figure 2. Catalytic Fe(-II) to Fe(0) cycle

To test this hypothesis, Fürstner *et al.* examined the viability of iron powder as a catalyst. Iron (0) powder, reduced in situ by reduction of FeCl$_3$ with potassium does not react with an aryl halide, and is therefore unable to enter the catalytic cycle. However, upon addition of a Grignard reagent the metal slowly dissolved to give a black solution that was then catalytically competent.[1]

Further support for this claim came from preparation of tetrakis(ethylene)ferrate, a well characterized Fe(-II) compound.[27] This complex is catalytically competent in cross-coupling reactions with efficiencies similar to the FeCl$_2$ catalysts synthesized *in situ*.[28]

Interestingly, in most cases, the iron precatalyst used has very little effect on the rate, yield, or selectivity of iron-catalyzed reactions.[1] Fe(acetylacetonate)$_3$ is most commonly used, as it is air stable and inexpensive. Only *sec*-alkyl Grignard reagents require the use of Fe(salen)Cl for effective reaction. Although iron-catalyzed cross-coupling reactions are not responsive to the catalyst, they are responsive to the nature of the nucleophile. Whereas all the organomagnesium reagents provided good yields, *n*-BuLi and Et$_3$Al afforded no cross-coupling product. Although the cause for this is unknown, Fürstner tentatively attributes this to the need to form a "rather covalent" bond between the Fe-M in the active

species.[14] The presence of a covalent bond between the Fe and the Mg has been observed in the X-ray crystallographic structure of [Cp(dppe)Fe(MgBr)·3 THF], a well defined complex with a iron-magnesium bond distance of 2.593 Å.[29]

The ability of iron-catalyzed cross-coupling reactions to couple alkyl Grignard reagents with aryl halides was exploited by Fürstner, *et al.* in the synthesis of the natural product R-(+)-Muscopyridine, a natural alkaloid. The key steps in this synthesis exploited the higher reactivity of triflates over chlorides in aryl-alkyl cross-coupling reactions. In the first step, the difunctional pyridine **8** was reacted with a Grignard reagent to yield product **9** and the dicoupled product in a ratio of 4:1. This reaction mixture was reacted with a second Grignard reagent to yield the crude product **10** in 80% yield. Ring closing metathesis followed by hydrogenation yielded the natural product in 46% yield from the pyridine.

Figure 3.
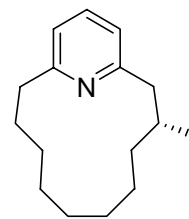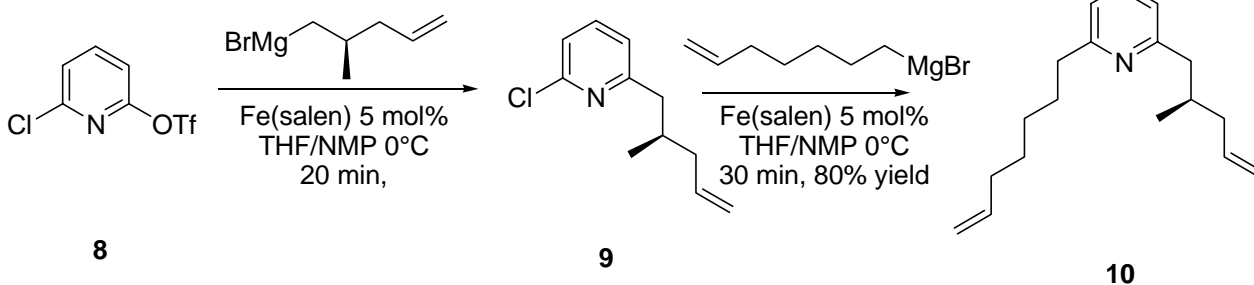(R)-(+)-Muscopyridine

Scheme 7. Key steps in the synthesis of (R)-(+)-Muskopyridine

CONCLUSIONS

Although the development of iron-catalyzed cross-coupling reactions is still in its infancy, unique characteristics and synthetic utility has already been demonstrated. The catalyst precursors are cheap, stable, non-toxic and environmentally friendly (when compared to palladium and nickel). The ability of iron complexes to conjoin alkyl halides with aryl Grignard reagents is a powerful addition to the substrate scope of cross-coupling reactions. Iron is also able to achieve comparable yields in alkyl-aryl and alkenyl-aryl cross-couplings, at lower temperatures and greatly reduced reaction times. However, iron is still limited by its dependence on the use of Grignard reagents. This has limited its utility in aryl-aryl cross-coupling reactions, and poses modest functional group restrictions. These limitations are consequences of the necessity of using magnesium as the organometallic donor, and are not inherent in the catalytic iron complex. There exists even greater potential if methods can be developed that allow other organometallic donors to be used. Presently, the substrate scope of iron-catalyzed cross-coupling reactions is complimentary to that of palladium-catalyzed cross-coupling reactions, and with further development will only become more synthetically useful.

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