JOC Perspective

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Low-Valent Iron-Catalyzed C−C Bond Formation−Addition, Substitution, and C−H Bond Activation

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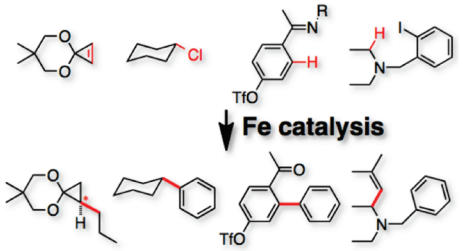

The use of iron as a catalyst for organic synthesis has been increasingly attracting the interest of chemists from economical and ecological points of view. While Fe(III) and Fe(II) catalysts have long been used as Lewis acids for synthesis, we have been interested in exploration of catalysis based on rather unexplored organoiron chemistry since the late 1990s. This Perspective summarizes a series of iron-catalyzed C−C bond formation reactions developed by us, which include (asymmetric) carbometalation of olefins, cross-coupling of alkyl halides, and activation of sp^2 and sp^3 C−H bonds.

I. Introduction: Why Iron?

Modern organic synthesis flourishes on the basis of the diverse reactivities of metal elements. Like oil, however, the supply of metallic elements is limited when viewed on the time scale of a century and is dependent on politics. Not only precious and rare metals will face diminished supply; common metals may also suffer from shortages of supply rather soon. Diminished supply will first result in soaring prices and finally in no supply. Thus, it is a good idea for chemists to explore the potential of catalysis by common metals, which may become the mainstream catalysts after all the palladium and ruthenium are gone. To take a more scientific view, it is always a good idea for chemists to study the properties of metals that have not received significant attention because we may discover new and exciting chemistry. About 10 years ago, we thought that iron was the metal of primary importance.

Iron is abundant. Iron is safe and environmentally benign. Iron can be a perfect catalyst for chemists.[1,2] Indeed, Fe(III) and Fe(II) have been widely used as a Lewis acid for the generation of carbocations[3] and radicals[4] and the activation of electrophilic substrates.[5] Fe(II) has also been used to reduce hydrogen peroxide to hydroxy radical species (Fenton reagent), which promotes hydrocarbon oxidation.[6,7] Most of the iron chemistry in the literature so far evolves around the high stability of Fe(III) species. Catalysis based on low-valent iron chemistry, organoiron chemistry in particular,[8] is rather rare.

II. Iron-Catalyzed (Asymmetric) Carbometalation

Toward the end of the 1990s, one of us (E.N.) started a research program on the use of low-valent iron as a catalyst for organic synthesis because of the paucity of useful applications. At that time, a few iron-catalyzed synthetic reactions of some generality had been reported, such as coupling between an alkenyl halide and a Grignard reagent pioneered by Kochi[9] and modified by others[10] and Fe(0)-catalyzed coupling of unsaturated compounds by Takacs and others.[11,12] Because asymmetric iron catalysis is rather limited in its scope and selectivity,[13] we decided to explore an asymmetric carbometalation reaction of olefins.[14−16] Perhaps we were too ambitious at that time because our initial work took us quite a long time and resulted in a reaction of rather limited applicability, namely, the asymmetric carbometalation of cyclopropenone acetals (Scheme 1).[17,18] Nonetheless, we are pleased with this reaction. To the best of our knowledge, this reaction is still the

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SCHEME 1. Carbometalation of Cyclopropenone Acetal with Grignard and Organozinc Reagents

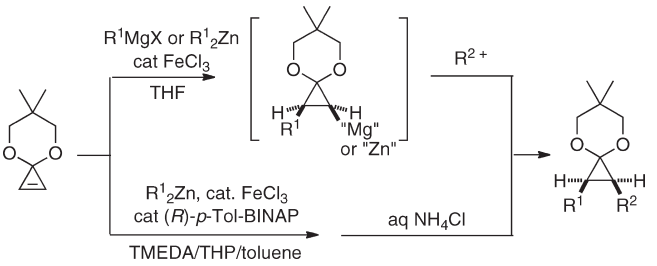


TABLE 1. Iron-Catalyzed (Asymmetric) Carbometalation (see Scheme 1)[a]

		3		
entry	organometallics R^1-metal	R^2	yield (%)	ee (%)
1	C_6H_5MgBr	H	96	
2	CH_2=$CHMgBr$	H	75	
3	CH_3MgBr	H	66	
4	$C_6H_5CH_2CH_2MgCl$	H	85	
5	$(C_5H_{11})_2Zn$	H	91	
6	$(^iPrOCOCH_2CH_2)_2Zn$	H	76	
7	C_6H_5MgBr	CH_2=$CHCH_2$	85[b]	
8	C_6H_5MgBr	CH_3	90[b]	
9	C_6H_5MgBr	$CH(C_6H_5)OH$	56[c]	
10	$(C_3H_7)_2Zn$	H	62	92
11	$(C_2H_5)_2Zn$	H	64	90

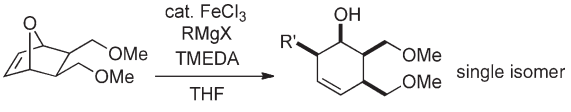
[a]Reaction conditions: $FeCl_3$ (3−5 mol %), THF or THF/toluene, −78 to −25 °C (entries 1−9); $FeCl_3$ (5 mol %), (*R*)-Tol-BINAP (7.5 mol %), TMEDA (2.5 equiv), toluene/THP, 0−25 °C (entries 10 and 11). [b]Diastereomeric ratio was >97:3. [c]A 1:1 diastereomer mixture for the benzylic chiral center.

only example of effective asymmetric C−C bond formation by low-valent iron species; it provides enantioselectivity as high as 90% enantiomeric excess (ee).[13,19]

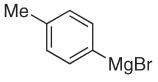
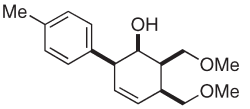
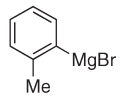
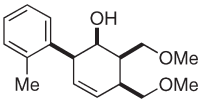
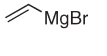
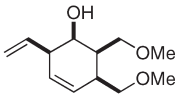
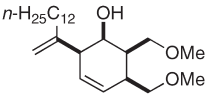
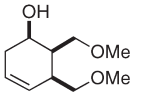
As shown by the selected examples in Table 1, various Grignard and organozinc reagents underwent syn-addition to the C=C double bond in the presence of a cheap pre-catalyst, $FeCl_3$, to give cyclopropylmagnesium and cyclopropylzinc species, which could be protonated or trapped by other electrophiles (entries 1−9). Furthermore, a carefully optimized ternary catalytic system consisting of $FeCl_3$, chiral diphosphine ((*R*)-Tol-BINAP) and achiral diamine (TMEDA) ligands allows enantioselective addition of dialkylzinc reagents with enantioselectivities of up to 92% (entries 10 and 11).

During this work, we also found that an iron catalyst promoted ring-opening reactions of an oxabicyclic alkene with a Grignard reagent (Table 2).[20,21] Aryl and alkenyl Grignard reagents effected ring-opening of the oxabicyclic alkene in the presence of $FeCl_3$ (5 mol %) and TMEDA (3 equiv) to give the corresponding arylated and alkenylated products in moderate to good yield with high regio- and stereoselectivity (entries 1−3). TMEDA greatly facilitated the reaction. Interestingly, when primary and secondary alkyl Grignard reagents were employed, β-hydride elimination and ring-opening reactions took place simultaneously. Thus, the reaction of n-$C_{14}H_{29}MgBr$ resulted in incorporation of a 2-tetradecenyl group into the product (entry 4), while *i*-PrMgBr underwent reductive opening of the oxabicyclic alkene (entry 5).

TABLE 2. Ring-Opening Reaction of Oxabicyclic Alkene with Grignard Reagent[a]



R = aryl, alkenyl, or 1° and 2° alkyl; R' = aryl, alkenyl, or H

entry	RMgX	temp.	time	product (yield)
1		25 °C	5 h	 (72%)
2		65 °C	1 h	 (75%)
3		65 °C	13 h	 (41%)[c]
4	n-$C_{14}H_{29}MgBr$	25 °C	1 h	 (54%)
5	*i*-PrMgBr	25 °C	1 h	 (92%)

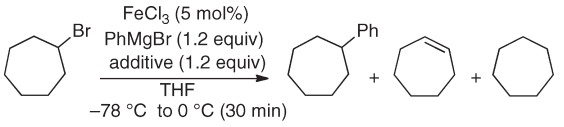
[a]The reaction was performed with $FeCl_3$ (5 mol %), RMgX (2 equiv), and TMEDA (3 equiv) in THF.

III. Iron-Catalyzed Cross-Coupling of Alkyl Halide

During the above studies, we discovered that TMEDA is an inexpensive, useful tool for tuning the reactivity of organoiron species. Further exploration led us to find that the iron−TMEDA combination is remarkably effective for the cross-coupling reaction of an alkyl halide and an aryl Grignard reagent (eq 3).[22] Despite the potential utility of such an iron-catalyzed $C(sp^3)-C(sp^2)$ coupling, the reaction suffered from a variety of problems, including low reactivity (especially secondary alkyl halides and alkyl chlorides) and side reactions (β-elimination, reduction, etc.).[23,24] A case study focused on the cross-coupling of cycloheptyl bromide and PhMgBr demonstrated that TMEDA suppresses the β-elimination reaction of the alkyl bromide, which is dominant in the absence of TMEDA (Scheme 2), and the reaction produces the desired cross-coupling product in good yield (Scheme 2). Other Lewis basic additives showed only marginal effects or even slowed the reaction. Further improvement was achieved by a modification of the operational procedure. Thus, by slowly introducing a mixture of PhMgBr and TMEDA into the reaction (typically over 20−60 min), the cross-coupling product was obtained in excellent yield and with high selectivity (97%).

Under the optimized conditions, primary and secondary alkyl iodides, bromides, and even chlorides were efficiently

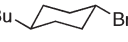
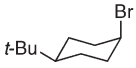
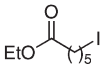
SCHEME 2. Effects of Additives on Iron-Catalyzed Cross-Coupling of Cycloheptyl Bromide and PhMgBr



additive =	none	TMEDA	Et_3N	NMP	TMEDA[a]
	5%	71%	3%	15%	97%
	79%	19%	78%	3%	3%
	0%	3%	0%	0%	< 0.1%

[a]PhMgBr/TMEDA was added at 0 °C over 60 min.

TABLE 3. Iron-Catalyzed Cross-Coupling of Alkyl Halides with Aryl Grignard Reagents[a]

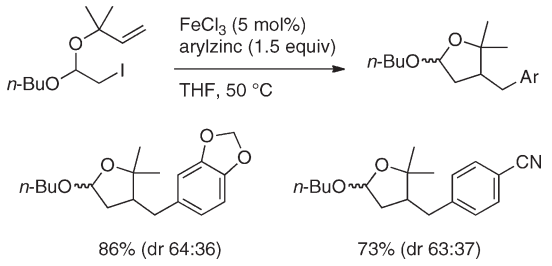
entry	halide	ArMgBr	product	% yield
1		Ar = Ph		99 (X = I)
2				99 (X = Br)
3				99 (X = Cl)
4		Ar = 4-$MeOC_6H_4$		99
5		Ar = 4-$CF_3C_6H_4$		67
6		Ar = 1-naphtyl		97
7		Ar = 2-MeC_6H_4		99
8				97 (X = I)
9	*n*-C_8H_{17}–X	Ar = Ph	*n*-C_8H_{17}–Ph	91 (X = Br)
10				45 (X = Cl)
11		Ar = 4-$MeOC_6H_4$	 (*trans*:*cis* = 96:4)	98
12		Ar = 4-$MeOC_6H_4$	 (*trans*:*cis* = 96:4)	98
13		Ar = 4-$MeOC_6H_4$		91

[a]Grignard reagent/TMEDA (1.2–2 equiv) was added over 20 min. Reaction temperature was 0 °C in entries 1, 2, 8, and 11–13, 25 °C in entries 3–7 and 9, and 40 °C in entry 10.

coupled with various aryl Grignard reagents at 0–25 °C (Table 3). In particular, the coupling reaction tolerates the presence of an ester group (entry 13). Concurrent publications on iron-catalyzed cross-coupling of alkyl halides and aryl Grignard reagents appeared shortly after our report from the Hayashi, Fürstner, and Bedford groups.[25] Hayashi developed a convenient procedure that employs $Fe(acac)_3$ as a precatalyst and refluxing Et_2O as the solvent. Fürstner demonstrated that a well-defined low-valent iron complex $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ serves as an excellent catalyst for the cross-coupling of alkyl bromides and iodides. Bedford found that an iron–salen complex uniquely promotes the alkyl–aryl coupling among other metal–salen complexes. Later, Cahiez reported that a certain tetraamine performs as well as TMEDA.[26,27]

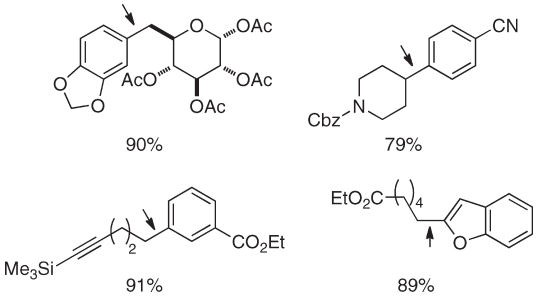
Several mechanistically intriguing observations have been made during the study. The reaction of (*S*)-2-bromooctane (99.5% ee) with PhMgBr took place with complete loss of optical purity. In addition, *trans*- and *cis*-1-bromo-4-*tert*-butylcyclohexane gave the cross-coupling product in the same diastereomeric ratio (*trans*/*cis* = 96:4, entries 11 and 12 in Table 3). These results indicate that the iron-catalyzed cross-coupling is not a simple nucleophilic substitution but involves a radical-like species that readily undergoes stereochemical mutation.[28]

SCHEME 3. Tandem Cyclization/Cross-Coupling with Arylzinc Reagent[a]



[a]The arylzinc reagent was prepared either from $ZnCl_2 \cdot TMEDA$ (1.5 equiv) and ArMgBr (3 equiv) or from ArZnX (1.5 equiv), Me_3SiCH_2MgCl (1.5 equiv), and TMEDA (1.5 equiv).

CHART 1. Representative Products of Iron-Catalyzed Coupling of Alkyl Halide and Arylzinc Reagent[a]



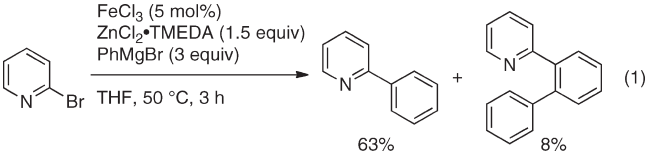
[a]Alkyl–aryl bonds formed by the cross-coupling are indicated by the arrows.

Our conjecture on the radical-like character of the organoiron species was reinforced by and exploited in a tandem cyclization/cross-coupling reaction. Thus, treatment of an iodoacetal bearing an olefin moiety with the iron catalyst and an arylzinc reagent (Ar_2Zn or $Ar(Me_3SiCH_2)Zn$) resulted in 5-*exo*-cyclization followed by cross-coupling to furnish a tetrahydrofuran derivative (Scheme 3).[29] In particular, the presence of a magnesium salt and TMEDA was essential for this reaction as well as for the normal cross-coupling reaction. As illustrated in Chart 1, the arylzinc coupling allows a wide range of functional groups in both alkyl halides and zinc reagents.[29,30]

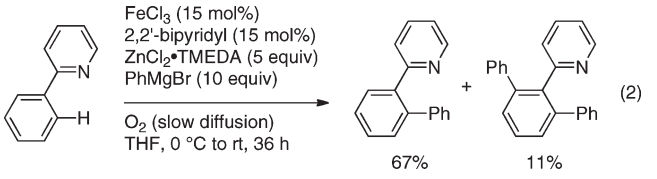
IV. Iron-Catalyzed Aromatic C–H Activation/C–C Bond Formation

As a natural consequence of the study, we then focused our attention on an iron-catalyzed biaryl coupling reaction because the scope of the reported iron catalysis was rather limited.[31,32] However, we switched our attention entirely away from the biaryl coupling when we discovered a hint of unusual C–H bond activation in an attempted cross-coupling of 2-bromopyridine with a diphenylzinc reagent (eq 1). The reaction produced the expected product, 2-phenylpyridine in 63% yield, and a small amount of a ternary coupling product in 8% yield. We surmised that the latter

was formed by an iron-catalyzed C−H bond activation reaction of the former.[33,34]



We spent about 2 years optimizing the reaction conditions to make this reaction synthetically viable. We first noted that none of the desired ternary coupling compound formed when the reaction was carefully repeated. Two issues became immediately apparent. First, the reaction produces a homocoupling byproduct, 2,2′-bipyridyl, which is an indispensable ligand for the C−H activation reaction. Second, molecular oxygen, which came inadvertently into the reaction vessel, serves as an oxidant to make the reaction catalytic. We then found that the way we introduced molecular oxygen to the reaction mixture significantly affected the product yield. Thus, excess oxygen killed the whole catalytic system, while a deficiency of oxygen resulted in incomplete reaction. A controlled supply of oxygen gas was essential to achieve high yield (eq 2; the second product formed by sequential C−H bond activation).[35] Although molecular oxygen is a convenient oxidant on a small scale, it is a hazardous reagent on a large scale. Furthermore, the reaction in eq 2 suffered from undesirable consumption of the diphenylzinc reagent due to homocoupling (i.e., formation of biphenyl) and oxidation (i.e., formation of phenol) and, hence, required a large excess of the zinc reagent.

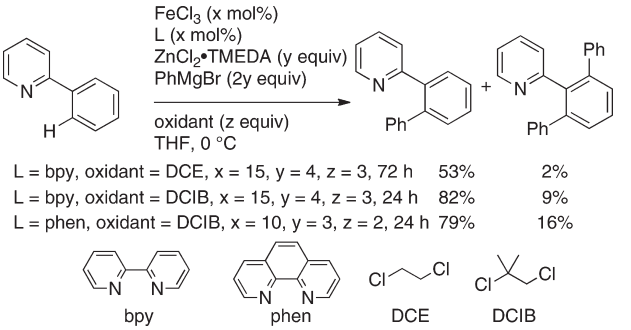


In search of a better oxidant, we examined a variety of organic, chalcogenide, and inorganic oxidants and eventually focused on 1,2-dihaloethanes.[36] The use of 1,2-dichloroethane (DCE) led to the production of the phenylation product in moderate yield, while the use of 1,2-dibromoethane gave only a trace amount of the product. The low yield is partly because of undesired homocoupling of the diphenylzinc reagent and cross-coupling between the dihalide and the zinc reagent (section III). Thus, a bulkier dichloride, dichloroisobutane (DCIB) was found to be the oxidant of choice (Scheme 4).[37]

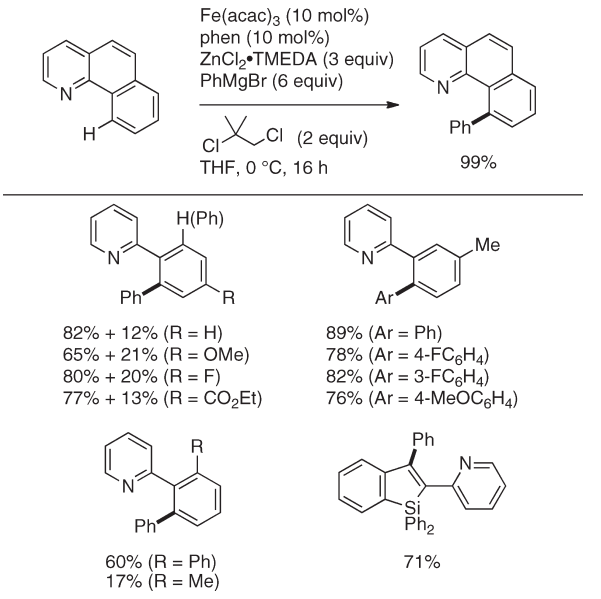
We found that this reaction requires a very intricate control of the reaction conditions. For instance, not only the aromatic bidentate nitrogen ligand and the dichloroalkane oxidant are required but also the use of the diphenylzinc reagent prepared from 1 equiv of $ZnCl_2 \cdot TMEDA$ and 2 equiv of PhMgBr was critical for the successful phenylation reaction. We observed much poorer yields or even no reaction when we used similar but different reagents such as $ZnCl_2$ + 2 PhMgBr (without TMEDA), PhMgBr (Grignard only), $ZnCl_2 \cdot TMEDA$ + PhMgBr (monophenylzinc), and Ph_2Zn (pure diphenylzinc).

Under the optimized conditions, various 2-arylpyridine derivatives were efficiently arylated by a diarylzinc reagent (Scheme 5). This C−H activation reaction features the use of

SCHEME 4. Effect of Dichloroalkane and Ligand on Iron-Catalyzed Phenylation of 2-Phenylpyridine



SCHEME 5. Direct Arylation of 2-Arylpyridine Derivatives

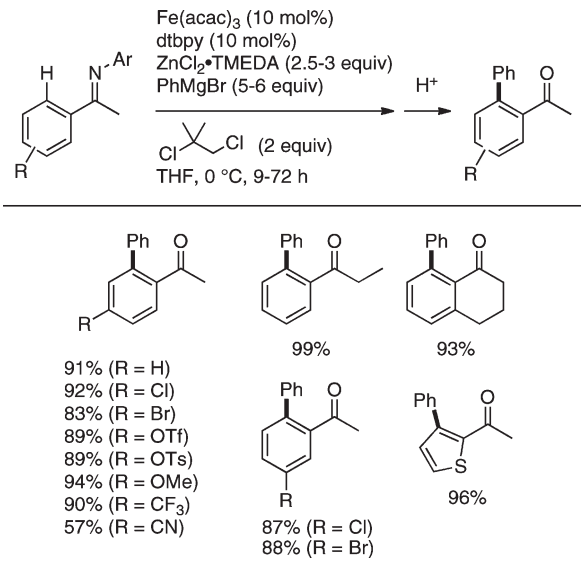


an inexpensive iron catalyst and very mild reaction conditions, 0 °C, much milder conditions than those by rare metal catalysts such as ruthenium, rhodium, and palladium (typically above 100 °C).[38,39] The observation attests to the fact that the very high reactivity of iron catalysts requires careful choice of reaction conditions. Notably, the reaction could be applied to a benzosilole derivative of interesting photophysical properties.[40]

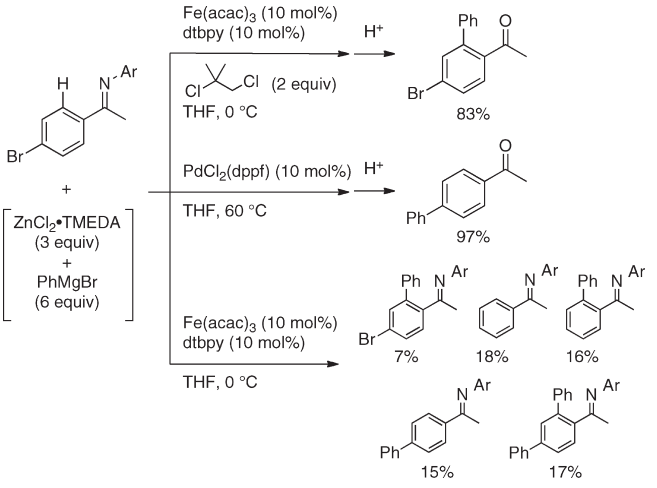
We found that nitrogen heterocycles (e.g., pyrimidyl and pyrazolyl groups) and imino groups serve as directing groups for the iron-catalyzed C−H activation. Among those substrates, the aryl imine groups are particularly attractive functional groups. Various aryl imines derived from the corresponding ketones and *p*-anisidine were phenylated under mild iron−dtbpy (dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl) catalysis (Scheme 6).[41]

This reaction is unique for its tolerance of electrofugal groups such as aryl bromide, chloride, triflate, and tosylate groups, which usually serve as excellent leaving groups in cross-coupling chemistry (see Scheme 6). An illustrative example is shown in Scheme 7. An aryl imine bearing a 4-bromo substituent underwent iron-catalyzed *ortho*-phenylation with retention of the bromide moiety, which could be

SCHEME 6. Iron-Catalyzed Direct Phenylation of Aryl Imines

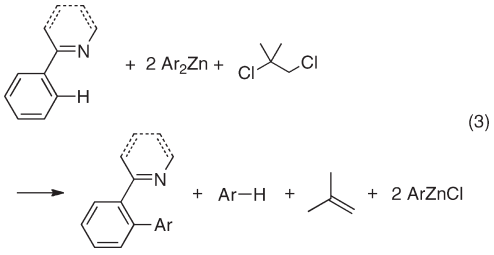


SCHEME 7. Reaction of 4-Bromoacetophenone Imine under Iron or Palladium Catalysis



subsequently arylated by conventional Suzuki−Miyaura coupling. On the other hand, palladium-catalyzed conditions expectedly effected cross-coupling at the bromide moiety. The presence of dichloroisobutane is critical. In its absence, the expected aryl−aryl coupling pathway competes with the C−H bond activation, and the reaction gave a mixture of products arising from direct arylation, reduction of the C−Br bond, and cross-coupling at the C−Br bond.

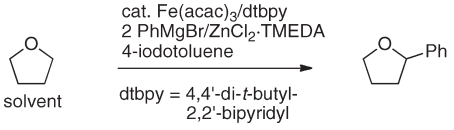
Though it is premature to discuss the mechanism of the reaction,[42] we describe the following observations that may help an understanding of the reaction pathway. First, a monoarylzinc reagent prepared from a 1:1 mixture of $ZnCl_2$·TMEDA and PhMgBr did not participate in the C−H activation reaction at all, indicating that only one of the two aryl groups on the diarylzinc reagent is reactive. Second, deuterium-labeling experiments revealed that 1 equiv of the zinc reagent is consumed for removal of the ortho hydrogen and 1 equiv for the arylation. Thus, the reaction by default requires 2 equiv of the zinc reagent, while a slight excess (2.5−3 equiv) is used in practice. Third, the dichloroalkane oxidant gives the corresponding olefin during the reaction. These observations indicate a plausible reaction stoichiometry as shown in eq 3.



(3)

V. Iron-Catalyzed Aliphatic C−H Activation

During the foregoing studies, we occasionally observed radical-like behavior of the organoiron species (Scheme 3). We decided to exploit this radical character to design of new synthetic reactions, for instance, the use of an organic radical intermediate for intramolecular hydrogen abstraction. Our expectation was fulfilled in an attempted cross-coupling of 4-iodotoluene and a diphenylzinc reagent (eq 4), which did not give the biaryl coupling product at all, instead producing a large amount of 2-phenyltetrahydrofuran. We considered that the following chain reaction took place, where the iron catalyst must be involved in the first and the third steps: reductive generation of an aryl radical from 4-iodotoluene, hydrogen abstraction from the 2-position of THF by the aryl radical, and coupling of the 2-tetrahydrofuranyl radical and a phenyl anion.



(4)

We exploited this unique reactivity for functionalization of otherwise unreactive sp^3 C−H bonds. We thus focused on the intramolecular 1,5-radical translocation strategy to form an α-amino radical, which was previously developed for pure radical reactions by Snieckus and Curran and later by Undheim.[43] They demonstrated that an aryl radical derived from an aliphatic amine bearing an *N*-halobenzoyl or halobenzyl (halogen = I or Br) group undergoes facile 1,5-hydrogen transfer to generate an α-amino radical, which can be trapped by an electron-deficient olefin. We envisioned that such an amine substrate bearing an internal trigger would undergo coupling at its α-position with an organometallic reagent under iron catalysis.

This hypothesis resulted in successful experimental implementation of a new iron-catalyzed cross-coupling reaction through activation of the α-C−H bond of an aliphatic amine with a Grignard reagent (Scheme 8 and Chart 2).[44] While α-branched amines are an important structural unit in bioactive compounds, there are only a limited number of methods that directly functionalize the α-position of aliphatic amines.[45,46] The synthetic method that we discovered is unique for its wide scope, which allows introduction of various aryl, alkenyl, and alkyl groups and for the use of inexpensive, nontoxic catalyst and reagent.

Our mechanistic hypothesis was supported by deuterium-labeling experiments. Crossover experiments using a mixture

SCHEME 8. Iron-Catalyzed α-Functionalization of Aliphatic Amine via C−H Activation through 1,5-Hydrogen Transfer

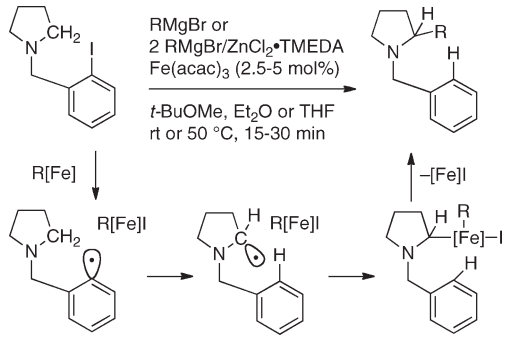
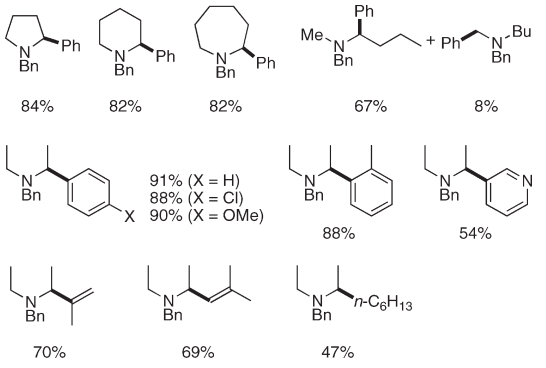
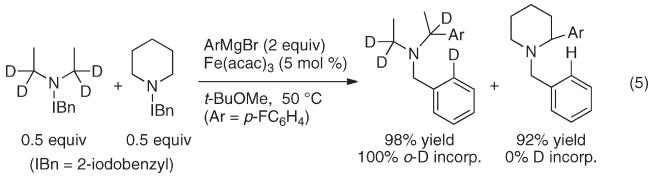


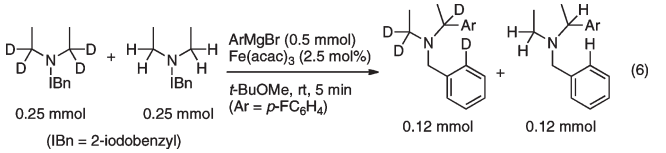
CHART 2. Products of Iron-Catalyzed α-Functionalization of Aliphatic Amines with Grignard Reagents[a]



[a] C−C bonds formed by the reaction are indicated by the thick bonds.

of deuterated and nondeuterated substrates unambiguously proved the intramolecularity of the hydrogen atom transfer (eq 5). In addition, no intermolecular H/D kinetic isotope effect was observed (eq 6), indicating that the 1,5-hydrogen transfer is not rate determining. This is reasonable in light of the high rate constant ($> 10^6$ s^{-1}) reported for the 1,5-hydrogen transfer step in the Snieckus/Curran reaction.[43a]





VI. Summary

In this Perspective, we described our foray into low-valent iron catalysis including a rationally designed asymmetric carbometalation reaction of olefins and a cross-coupling reaction of alkyl halides and how these studies led us serendipitously to develop iron-catalyzed $C(sp^2)$−H and $C(sp^3)$−H activation/C−C bond formation reactions.[47,48] Our C−H activation reactions not only featured the use of iron as a catalyst for synthesis, but also suggested new directions of organic synthesis. The use of Grignard or organozinc reagents for C−H bond activation has thus far been unusual. The direct arylation of aromatic C−H bonds is attractive for the mild reaction conditions (i.e., 0 °C). The uniquely effective dichloroalkane oxidant is mechanistically intriguing. Expansion of the substrate scope and development of simpler catalytic systems will be the next target of our studies. The cross-coupling of the α-C−H bond of aliphatic amines and Grignard reagents is unique for its merger of radical and organometallic chemistry for C−H bond activation.[47a] This concept will find further applications. It is still unclear at this time whether we can extend the iron catalysis beyond C−H bond activation toward new possibilities of organometallic chemistry. Nonetheless, we have considerable faith that further exploration of low-valent iron catalysis will lead to a number of new discoveries and development of cost-effective and environmentally benign synthetic methods.

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