

Iron Catalysis in Organic Synthesis: A Critical Assessment of What It Takes To Make This Base Metal a Multitasking Champion

Alois Fürstner*

Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim/Ruhr, Germany

ABSTRACT: The current status of homogeneous iron catalysis in organic chemistry is contemplated, as are the reasons why this particular research area only recently starts challenging the enduring dominance of the late and mostly noble metals over the field. Centered in the middle of the d-block and able to support formal oxidation states ranging from $-II$ to $+VI$, iron catalysts hold the promise of being able to encompass organic synthesis at large. They are expected to serve reductive as well as oxidative regimes, can emulate “noble tasks”, but are also able to adopt “early” transition metal character. Since a comprehensive coverage of this multidimensional agenda is beyond the scope of an Outlook anyway, emphasis is laid in this article on the analysis of the factors that perhaps allow one to control the multifarious chemical nature of this earth-abundant metal. The challenges are significant, not least at the analytical frontier; their mastery mandates a mindset that differs from the routines that most organic chemists interested in (noble metal) catalysis tend to cultivate. This aspect notwithstanding, it is safe to predict that homogeneous iron catalysis bears the chance to enable a responsible paradigm for chemical synthesis and a sustained catalyst economy, while potentially providing substantial economic advantages. This promise will spur the systematic and in-depth investigations that it takes to upgrade this research area to strategy-level status in organic chemistry and beyond.



■ INTRODUCTION

Heterogeneous iron catalysis has arguably changed the world.¹ This bold statement reflects the fact that the Haber–Bosch process, which uses iron-based catalysts to convert molecular nitrogen into ammonia, is the chemical basis for a sustained food production on which the exponentially growing world population has to live (and try to fight malnutrition). Of similar economic relevance, though arguably less vital, is the Fischer–Tropsch process that allows basically any carbonaceous material to be converted into liquid fuel. Originally designed for coal processing, natural gas is the dominant feedstock in the current economic and political context, but renewable (waste) carbon sources are expected to gain importance in the future. Finally, reference is made to the water gas shift reaction for large-scale hydrogen production and CO management. In view of these selected examples, the claim that the subsistence of mankind depends on iron catalysis is not hyperbolic.

The importance of *homogeneous* iron catalysis, in contrast, is not anywhere close. Actually, a look into the common chemical databases shows that this field, despite a long tradition, has become a focal research area only recently as evident from the exponential rise in the number of publications after the turn of the millennium. As timely and comprehensive reviews are available with thousands of citations,^{2–7} this short Outlook article can focus on the reasons why that is so, as well as on the factors that might help sustain the current momentum. On the longer run, many obvious, if not even trivial, arguments speak for iron catalysis at large:

- This metal, its oxides and many of its salts are readily available, cheap, and relatively nontoxic.⁸ Currently, iron is considered by the regulatory authorities a “metal with minimum

safety concern”; 1.300 ppm residual iron is deemed acceptable in drug substances.⁹ This status represents a distinct advantage when compared with the ≤ 10 ppm prescribed for most other transition metals. In any case, iron catalysis holds the promise of enabling a responsible paradigm for chemical synthesis and a sustainable “catalyst economy” while providing potential economic advantages at the same time.

- Iron is located in the center of the d-block, just above ruthenium as arguably one of the most versatile central metals in contemporary catalysis research; iron is hence “early” and “late” at the same time and should therefore be able to encompass a truly wide range of different chemistries; indeed, a look into the cited reviews and monographs shows that hardly any area of organic synthesis is—at least in principle—beyond its reach.^{2–7}

- Iron spans *formal* oxidation states ranging from $-II$ to $+VI$ and is hence useful in reductive and oxidative manifolds alike.

- The Lewis acidity of iron varies from fairly modest to very high; this property is strongly correlated with the oxidation state and hence tunable not only by the choice of ligands. Although iron-catalyzed reactions of the Friedel–Crafts type are well established,^{2–7} the pronounced Lewis acidity of high-valent iron still provides ample room for discovery.¹⁰

- Iron cations binds well to many N- or O-based ligands as well as to N-heterocyclic carbenes and cognate donors; this affinity often allows phosphines and relatives to be avoided, which can entail additional cost-, labor-, and environmental savings.

Received: September 14, 2016

Published: October 27, 2016

•None of the biocatalysts evolved by nature uses any noble metal, whereas iron-dependent enzymes are vital for all forms of life;¹¹ they effect a host of transformations of intriguing beauty, many of which mankind still has a hard time to emulate.

•Even a cursory look at the role of iron-dependent enzymes shows that redox chemistry is arguably the single most important chemical function, although evolution apparently appreciates the inherent Lewis acidity of this metal too;¹¹ the wisdom of the ages most likely heralds the areas in which synthetic iron catalysts are expected to excel.

•The organometallic and coordination chemistry of iron, as relevant for homogeneous catalysis, remains a wide-open field of research with enormous opportunities for discovery and innovation. Though challenging, iron chemistry holds the promise of providing academic rewards while paying utilitarian dividends.¹²

These arguments leave little doubt that homogeneous iron catalysis (and that of some of its base metal neighbors such as manganese and cobalt) will massively gain importance in organic chemistry in the not too distant future; a similar or even bigger impact is expected in the areas of small molecule activation, polymerization, and electrocatalysis that are not explicitly covered in this account.^{6,13–15} It is reasonable to assume that base metal catalysis in general and iron catalysis in particular will eventually challenge the enduring dominance of the more “noble” metals¹⁶ over the field of homogeneous catalysis. A look into timely monographs shows that some of the scarcest, most expensive, and often physiologically suspect transition metals currently hold a surprisingly big stake (Pd, Ru, Rh, Ir, Os, Pt, Au, etc.);¹⁷ the cohort is further complemented by elements such as Cu and Ni, which, although not strictly “noble” themselves, show somehow related reactivity. As a group, these elements provide advantages that outweigh a number of serious drawbacks: high costs, the risk of “political” price fixing as a consequence of massively imbalanced global distribution,¹⁸ a potentially nonsustained supply, and/or precarious toxicological and environmental properties. Such factors are subordinate in academic settings and may not be critical for processes either that operate on relatively small scale but provide much added value. It is, however, much less intuitive why even the production of commodities or fine chemicals heavily relies on the use of noble metal catalysts:^{17,19} hydroformylation (Rh), hydrosilylation (Pt), Wacker-oxidation (Pd), or acetic acid production (Rh, Ir) are striking cases; even cross coupling (Pd) and asymmetric hydrogenation (Ru, Rh, Ir, etc.) increasingly expand their reach beyond specialty and pharma applications. The situation seems even more paradoxical if one considers that rhodium catalysis has essentially replaced earlier cobalt-based technology for mass-scale hydroformylation, just as acetic acid production using expensive noble metals superseded Fe-, Co-, or Ni-based ancestor methodologies.

■ AN ANALYSIS IN “AL FRESCO” STYLE

The reasons for the supremacy of the noble metals in contemporary homogeneous catalysis must therefore be innately chemical in origin. The enormous breath and diversity of this field, however, spoil all attempts at condensing the pros into a few general statements. Nevertheless, one probably cannot help but say that the compliance of most noble metal catalysts with two-electron transfer processes is a pre-eminent factor working in their favor.²⁰ Likewise, the affinity of the polarizable late metals to π -bonds is a distinct advantage as long as alkenes,

These arguments leave little doubt that homogeneous iron catalysis (and that of some of its base metal neighbors such as manganese and cobalt) will massively gain importance in organic chemistry in the not too distant future.

arenes, and alkynes represent the major feedstocks of an oil-based chemical industry.²¹

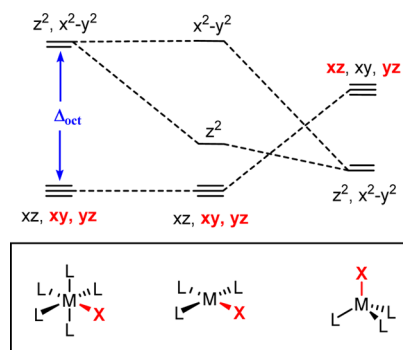
Having said this, I appreciate that any statement at this level of generalization is necessarily imprecise. Take, for example, palladium-catalyzed C–C and C–X cross coupling: one can argue that the perhaps single most important factor for the overwhelming success and economic viability of this type of transformation is the pronounced preference of palladium for two-electron redox steps. A knowledgeable adept, however, will rightfully object that this argument overlooks, for instance, the beneficial role that formal Pd(+1) or Pd(+3) plays in certain cases.^{22,23} Likewise it is tempting to describe metal-catalyzed hydrogenation reactions as proceeding via faithfully executed two-electron oxidative addition/reductive elimination steps or as not involving any redox business at all (outer-sphere hydrogenations).¹⁷ Again, this synopsis is wrong in that it fails to acknowledge that hydrogenations via radical intermediates are a well-proven physical reality;¹⁷ yet, it tacitly conveys the message that their practical importance is certainly below par.

■ BLESSING AND CURSE: THE REDOX BATTLE

Although the claim that the preference for redox-neutrality or even-numbered redox manifolds is a major asset of many noble metal-based processes has to be taken “*cum grano salis*”,²⁴ it helps to carve out some of the challenges that base-metal catalysis is posing. Iron complexes are certainly capable of engaging in two-electron transfer processes, but single electron transfer (SET) is competitive and, in many cases, preferred. Any attempt at using iron catalysts to emulate chemical behavior more befitting the noble metals has to cope with competing SET. In conceptual terms, however, it is difficult to gain control over this propensity: while chemists are good at tuning redox potentials by proper choice of ligands, few strategies are currently known that allow the inclination toward a certain type of redox action ($1e^-$ versus $2e^-$) to be altered, which is largely a derivative of a given metal’s innate electronic structure.

One way to disentangle the intricate redox behavior of iron addresses the splitting (Δ) of the d-orbital energy levels that controls the electronic occupancy (Scheme 1). The major determinants are the coordination geometry and the nature of the chosen ligands: strong field ligands lead to larger splitting, in particular, in the octahedral ligand field, and hence favor electron pairing and the formation of low-spin complexes.²⁵ Although a detailed discussion is beyond the scope of this article, it is certainly not by chance that nature incorporates strong-field ligands such as CO or CN^- into iron-containing hydrogenases in order to process the consumed hydrogen in ionic rather than radical form.^{11,26} This example nicely showcases the eminent importance of ligand field theory in the realm of (third-row) base metal catalysis.

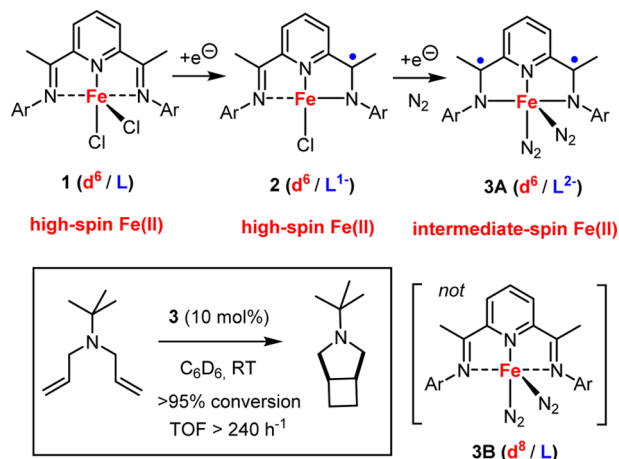
Scheme 1. Basic Ligand-Field Splitting Pattern in Octahedral, Square-Planar, and Tetrahedral Iron Complexes^{27a}



^aThe red labels indicate the d-orbitals of proper symmetry for π -interactions with the ligand X; note that the z-axis is vertical on the page.

An alternative concept for managing redox events relies on metal/ligand cooperativity (Scheme 2).^{28,29} “Non-innocent”

Scheme 2. A Well-Studied Example Illustrating the Concept of Metal/Ligand Cooperativity; Application of 3 to an Intramolecular [2 + 2] Cycloaddition^a



^aAr = 2,6-di(isopropyl)phenyl.

ligands can largely take over the actual electron transfer business; as a consequence, spin density gets delocalized in the periphery. By virtue of the resulting “diarmed” π -radical character, the early transition metal center basically maintains its oxidation state during the reaction and hence gains a certain degree of “nobility”, whereas the ligand environment acts as electron reservoir; a possible price to pay is that the ligand becomes potentially more vulnerable. Complex 3 formed by stepwise reduction of 1 is deemed instructive (Scheme 2):³⁰ while conventional electron counting sees an Fe(0) center coordinated to a di-imine ligand (resonance extreme 3B), in-depth spectroscopic and theoretical studies showed that it is better viewed as an Fe(II) species (d^6) comprising a delocalized ligand diradical (resonance extreme 3A; the spin singlet ground state ($S = 0$) is due to antiferromagnetic coupling of the iron and ligand triplet state). In keeping with this analysis, 3 and relatives served as catalysts for hydrogenation, hydrosilylation, cycloaddition, and cycloisomerization reactions,

all of which are usually performed with the aid of noble metals otherwise.^{31–34}

Any attempt at using iron catalysts to emulate chemical behavior more befitting the noble metals has to cope with competing single electron transfer.

This particular example is well understood, but most other complexes have not been scrutinized nearly as carefully. In this context it is also important to recognize that oxidation states are not unambiguous, while spin states are. The distinction between the formalism of organometallic conventions and physical reality needs perhaps to be more widely appreciated by the practitioners.

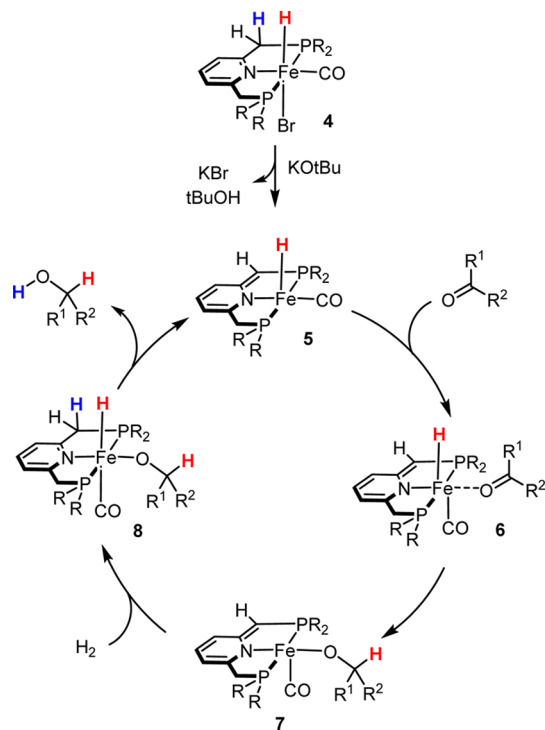
The ability to exert redox activity is obviously not limited to the particular di-iminopyridine ligand present in 3, which leaves considerable room for creative design.^{35–38} Therefore, it is hardly surprising that related ligands have already served various types of transformations well.^{39–42} Even the ubiquitous CO or isonitrile ligands can “iron out” changes in charge density at the central metal, at least to some degree.^{43,44} Once again, nature is the true master of ligand-centered electronic events which it uses to ensure the proper functioning of many metalloenzymes, not least those comprising iron–sulfur clusters as cofactors.¹¹ At the meta-level, the concept of “metal/ligand cooperativity” advocates a holistic view on coordination chemistry, certainly when it comes to redox-active base metal complexes: rather than dissecting a given complex into the “reactive” metal center and a sphere of “ancillary” ligands, it must be seen as an ensemble to be described in terms of molecular orbitals that encompass the center and periphery.

A different flavor of iron/ligand cooperativity is manifest in the pincer complex 4 (Scheme 3)⁴⁵ and the cyclopentadienone complex 10 (Scheme 4).^{46–48} These innovative catalysts for carbonyl (imine) hydrogenation or hydrosilylation operate by heterolytic rather than homolytic bond cleavage. The splitting of H_2 into a proton and a hydride and their subsequent delivery are driven by peculiar ligand properties: the pyridine scaffold of 4 or the cyclopentadienone unit of 10 is able to switch between an aromatic and a dearomatized state. Moreover, it is noteworthy that either complex comprises additional strong-field ligands that foster splitting of d-orbital energy levels and hence favor low-spin iron configuration. Asymmetric variants of such systems have also been described.⁴⁹ Equally noteworthy is the fact that high turnover numbers have been reached in some iron-based (transfer) hydrogenations,⁵⁰ which is a “must” in view of the high standards in this particular research field.

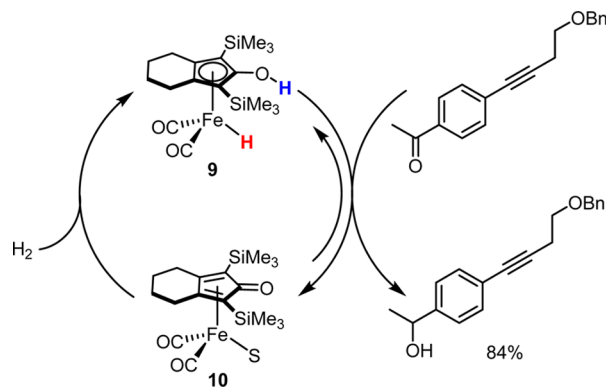
If one accepts metal/ligand cooperativity as a means to impart “nobility” on iron, it is fairly obvious that metal/metal cooperativity and cluster catalysis are other possibilities to consider.⁵¹ If two electronically coupled (base) metal centers individually exert single-electron transfer events, the net outcome resembles a two-electron process occurring at a single site.⁵²

Alternatively, the combination to two different (base) metal centers with dissimilar electron affinities can be used to enforce heterolytic bond cleavage. Actually, many preparative procedures are known in the literature that combine iron precatalysts with more noble additives; unfortunately, however, it is usually unknown whether these empirical recipes exploit such cooperativity effects or not.^{53–57} Likewise, a synergy between the active iron

Scheme 3. Carbonyl Reduction via Heterolytic Activation of Dihydrogen Using a Catalyst That Switches between Aromatic and Dearomatized States



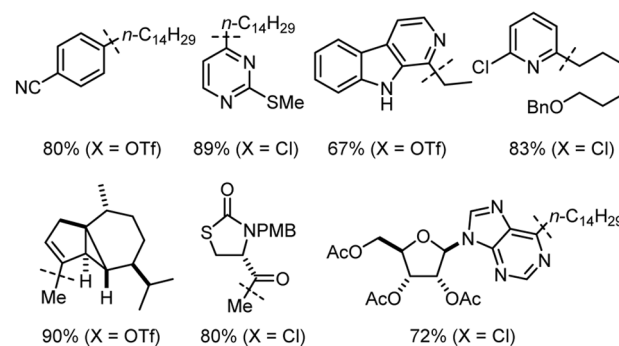
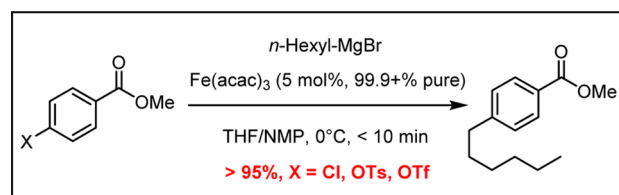
Scheme 4. Heterolytic Cleavage of Dihydrogen with the Aid of Knölker's Catalyst; Application to a Chemoselective Carbonyl Reduction That Leaves an Alkyne and a Benzyl Ether Untouched



species and Mg^{2+} cations might well play a role in iron-catalyzed cross coupling which continues to work best with Grignard reagents as the nucleophilic partners. Although first examples of iron-catalyzed cross coupling predate the use of nickel and palladium,^{58–60} this chemistry started to flourish much later (Scheme 5).^{61–63} Many important advances have been made, including a growing number of studies from industrial laboratories which try to harness the advantages that the use of iron catalysts for such a “noble task” can provide.^{64,65} However, only in a few special cases is the mechanistic fog about to lift (see below). More generally speaking is the discrepancy between empirical knowledge and a deeper understanding not untypical for the field at large.

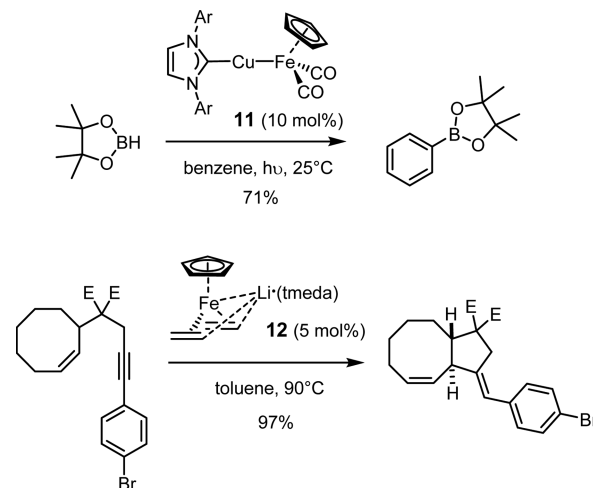
Mechanistically more convincing cases for heterobimetallic catalysts, in which an iron center acts in concert with a

Scheme 5. Iron-Catalyzed Cross Coupling of Alkyl-Grignard Reagents with (Hetero)aryl, Alkenyl, and Acyl Halides or Sulfonates



second element, are manifest in recent reports on the use of $[\text{Cp}(\text{CO})_2\text{Fe}-\text{Cu}(\text{IPr})]$ (**11**) as catalyst for C–H borylation and stereochemically unorthodox *trans*-reductions of alkynes (even though Ru seems more adequate in this case) (Scheme 6).^{66–70}

Scheme 6. Two Examples for the Use of Iron-Containing Heterobimetallic Complexes as Catalysts



Another well-defined bimetallic iron complex is $[\text{CpFe}(\text{C}_2\text{H}_4)_2]-[\text{Li}(\text{tmeda})]$ (**12**), which catalyzes Alder-ene reactions as well as $[4 + 2]$, $[5 + 2]$ and $[2 + 2+2]$ cycloadditions and therefore represents a cheap alternative to the Ru or Rh complexes commonly used for such purposes.⁷¹ **12** was shown to operate via ferracyclic intermediates formed upon canonical two-electron transfer; to which extent the escorting lithium cation assists in sustaining this manifold remains to be elucidated.

■ LIGAND ALLURES

In addition to the particular iron/ligand cooperativity manifest in the examples outlined above, a few additional aspects of the coordination chemistry of iron relevant for homogeneous

catalysis need to be briefly mentioned. It is important to recall that water exchange at $[\text{Fe}(\text{OH}_2)_6]^{2+}$ is on the order of 10^8 faster than that at $[\text{Ru}(\text{OH}_2)_6]^{2+}$,⁷² although the water ligand itself is perhaps not overly relevant in the current context, this kinetically well-studied example pinpoints a few challenges to be met in ligand design. Rapid loss of an ancillary ligand meant to control the electronic status and/or the selectivity of a metal-catalyzed transformation is obviously detrimental; it is unnecessary to say that premature ligand loss can also result in fast catalyst decomposition and hence obviate economic viability.

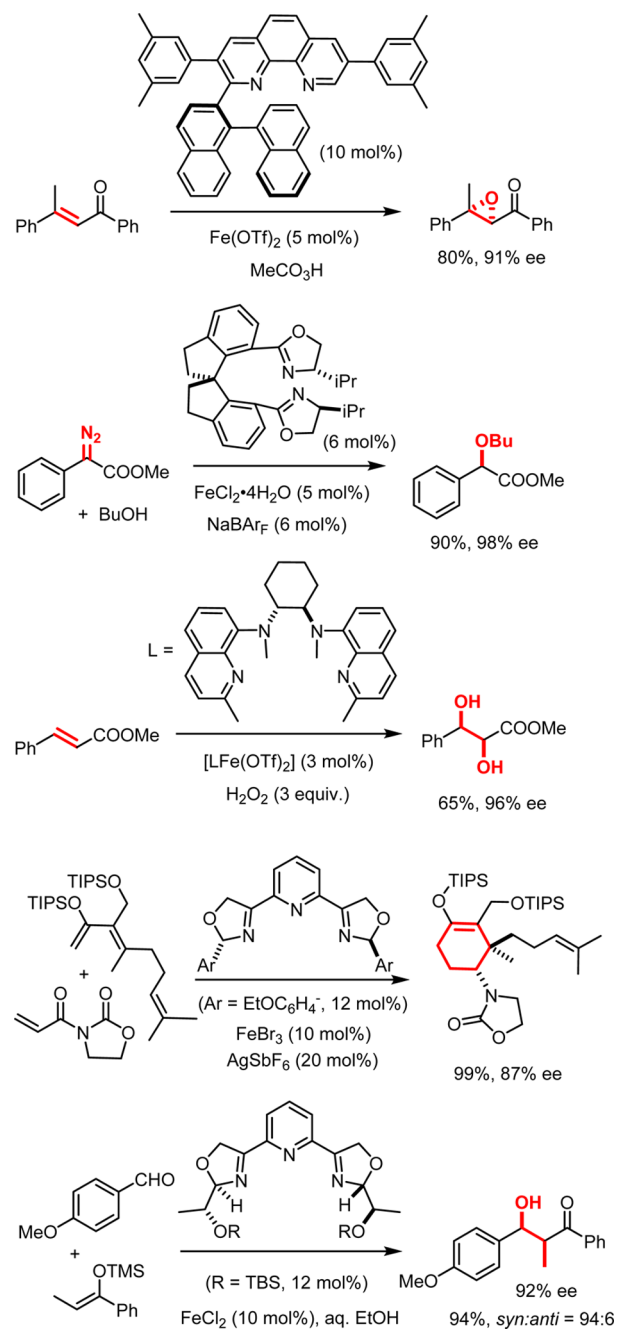
If one accepts metal/ligand cooperativity as a means to impart “nobility” on iron, it is fairly obvious that metal/metal cooperativity and cluster catalysis are other possibilities to consider.

The common countermeasure is recourse to the chelate effect and/or the use of π -acceptor ligands that favor effective back-bonding from the metal to its ligand environment. The noninnocent pincer ligands discussed in the previous section fall into this category. The prominence of the porphyrin scaffold in nature’s iron chemistry illustrates this aspect even more clearly: this framework combines kinetic inertia with fairly high chemical stability, which is particularly important in oxidation catalysis where ligand degradation is a most serious threat. With this in mind it is easy to appreciate why asymmetric oxidation catalysis with the aid of small-molecule iron complexes has its roots in the design of effective chiral porphyrin complexes.^{73,74} Another striking illustration for the stability that porphyrins (or phthalocyanines)⁷⁵ can impart is a cyclopropanation protocol in which diazomethane is generated in situ in the presence of the iron catalyst in a biphasic mixture, one phase of which consists of no less than 6 M aqueous KOH.⁷⁶

The need to ensure permanent residency of a chiral ligand is certainly a major reason why chelating and π -accepting ligands also feature prominently in asymmetric iron catalysis.^{74,77} The examples shown in Scheme 7 illustrate the point.^{78–82} Although this field has made much progress during the past decade, it still provides ample room for improvement and generalization.

Finally, a special allure of the metal/ligand interplay deserves brief mentioning. Iron cations are surprisingly flexible with regard to the coordination numbers and geometries that they support; in addition to the common square-planar, tetrahedral, trigonal-bipyramidal, and octahedral settings, low-coordination numbers are frequently encountered.^{83,84} The formation of tricoordinate complexes is fairly easy to enforce with the aid of β -ketiminates (or related ligands) bearing sufficiently bulky substituents in the periphery, which prevent dimerization of the resulting complexes, impart solubility in the usual organic solvents, and often leave room for only a single, fairly small third ligand to complete the coordinate sphere. By virtue of their bite angle Θ of $\sim 95^\circ$, the resulting complexes can lose all orbital degeneracy (Scheme 8):²⁷ this fact, in turn, implies that the chemical character of a three-coordinate iron cation can largely differ from that of iron of the same oxidation state in an octahedral environment, particularly if made of strong-field ligands. Generally speaking does a low coordination number

Scheme 7. Enantioselective Iron Catalysis Made Possible by Chelating Chiral π -Acceptor Ligands

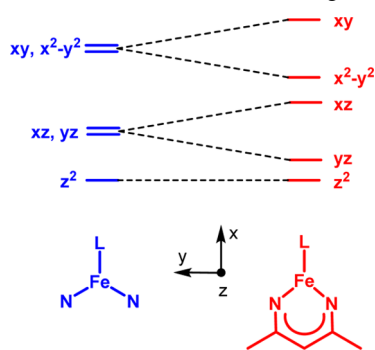


emphasize iron’s “early” transition metal character, whereas an appropriately engineered octahedral ligand field is one way to confer “nobility” onto this element (see above). The ability to strongly modulate the chemical character of iron solely by changing the coordination number is an innovative concept for reaction design that has not yet been given the attention that it may deserve.²⁷

THE ANALYTICAL FRONTIER

The frequent intervention of high spin and open-shell intermediates render mechanistic and kinetic investigations into iron catalysis tremendously difficult; the problems are potentiated by the oftentimes very limited stability of (organo)iron complexes in low or high oxidation states. An additional challenge arises

Scheme 8. Enforcing Orbital Degeneracy by Low Coordination Numbers and Small Bite Angles²⁷



from the intriguing possibility of spin change along a reaction coordinate (“two-state reactivity”).^{85,86} Even though paramagnetic complexes are amenable to NMR, this technique is by no means routine. On the other hand, open-shell systems lend themselves to investigation by electron paramagnetic resonance (EPR), Mößbauer spectroscopy, magnetic measurements, electrochemistry, X-ray absorption and emission spectroscopies, etc.,⁸⁷ which can provide very accurate portrayals of the species of interest but need serious investment into equipment and training. Suffice it to say that the interpretation of such spectra often requires calibration with model compounds and/or high-level computational studies, which themselves are by no means trivial for open-shell compounds.⁸⁸ This challenge notwithstanding, systematic forays into iron catalysis almost certainly mandate a comprehensive approach that combines preparative work, advanced spectroscopy, and theoretical chemistry at a level not commonly practiced when dealing with noble metal catalysts. It is safe to predict that this field will greatly benefit from a firm interface with bioinorganic chemistry with its long and successful holistic traditions.¹¹

To illustrate this aspect, reference is made to recent studies into the mechanism of iron-catalyzed cross coupling, which have been subject to considerable debate in the past. Unlike their renowned palladium counterparts, it was proposed early on that such reactions may not follow a uniform mechanism,^{63,64} rather, the actual pathway is strongly dependent on the substrate/reagent combination and the chosen ligands. Mechanistic investigations, however, struggle with the characterization of pertinent organoiron intermediates which are exceptionally labile. At least for the case of MeMgX as the nucleophilic partner, however, a combined crystallographic, spectroscopic, and kinetic approach recently provided a consolidated picture. In the essence, $[\text{Fe}_3\text{Me}_{12}]^-$ was identified as the most likely candidate accountable for methyl transfer to an alkenyl halide partner;⁸⁹ interestingly, this species is an ate-complex (remotely related with cuprate chemistry) and a mixed-valent iron cluster at the same time. This impressive study complements earlier work that had already pointed at iron-ate species as possible intermediates whenever groups unable to undergo β -hydride elimination are to be transferred.^{90–93} Related studies were devoted to the mechanism of phenyl transfer to alkyl halide partners catalyzed by iron complexes endowed with phosphine ligands:⁹⁴ while an Fe(0) as well as an Fe(II) species were both found able of effecting the C–C coupling step, their kinetic competences proved largely different. In contrast, Fe(I) complexes, which were prominently advocated elsewhere as causative agents,^{95,96} basically proved incompetent. While these results are deemed representative for the intricacies of mechanistic

organoiron chemistry, the chosen integral approach to unravel the details is exemplary for future investigations into this unusually demanding field of research.

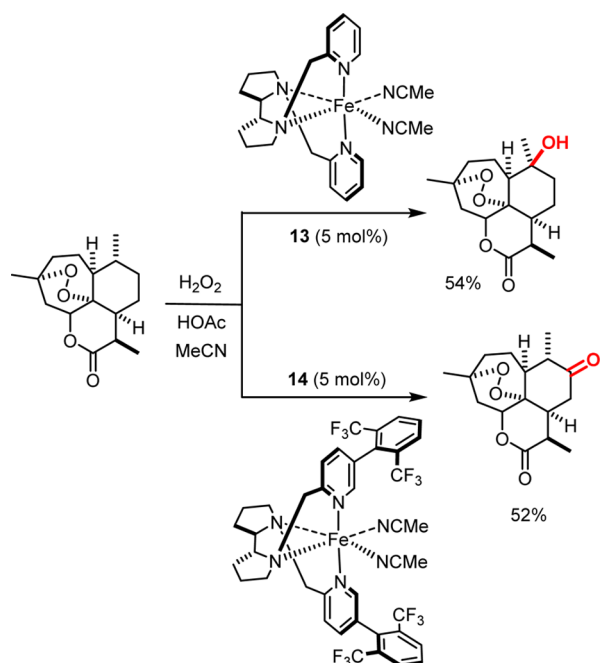
■ GO WITH THE FLOW

As long as crude oil is mankind’s preferred carbon source, alkenes, arenes, and alkynes will be the basic feedstocks of chemical industry. This material basis, in turn, favors the use of polarizable and inherently π -affine late transition metal catalysts. However, the arsenal will have to adapt as renewable raw materials eventually become more important. Base metals are perhaps better apt to address the challenges posed by building blocks that are overfunctionalized primarily with O- and N-substituents, which living nature can deliver in quantity; iron catalysis at large will benefit from such a changing situation.

In a somewhat orthogonal sense, paradigm changes in the science of synthesis itself are also likely going to favor base metal catalysis on the longer run. While our ways of making peptides, saccharides, or polyketide natural products—at the strategy level—are not very different from nature’s roster, other areas basically lack any such correspondence. Biosynthetic pathways for terpene synthesis, for instance, comprise distinct phases which largely separate the assembly and cyclization of the carbon backbone from its subsequent functionalization; to this end, nature has evolved oxidoreductases that allow functional groups to be stitched onto the rim of a given hydrocarbon skeleton with breathtaking regio- and stereoselectivity. This unrivalled ability to “metabolize” an existing carbon framework in a well-controlled manner differs fundamentally from what most chemical terpene syntheses are exercising, which usually construct the target skeleton while manipulating strategically positioned functional groups. Such practice was mandatory as long as no artificial catalysts able to mimic the function of oxidoreductases were available. The past decade, however, has seen a number of designer catalysts that are able to effect C–H functionalizations with high precision at different sites of a hydrocarbon chain even in the absence of directing groups; many of them are iron-based and able to use commodity oxidants such as H_2O_2 .^{97–100} They are thought to operate in a biomimetic fashion in that well-defined high valent iron species are responsible for hydrogen abstraction; the reactions are ligand-controlled and hence amenable to tuning (Scheme 9).^{101–103} Ascent of such catalysts to the strategy level impacts on more than just the logic of natural product synthesis: late-stage functionalization, when decoupled from scaffolding, is equally valuable for diversity-oriented programs in the life sciences in general and medicinal chemistry in particular. Overall, oxidation chemistry is arguably the single most important area to benefit from a stronger commitment to iron catalysis; the prominence of iron-dependent oxidizing enzymes in nature cannot be misleading and a now rapidly growing number of success stories using small-molecule designer catalysts augurs well for the future development of this particular field.

In a somewhat orthogonal sense, paradigm changes in the science of synthesis itself are also likely going to favor base metal catalysis on the longer run.

Scheme 9. Example of a Catalyst-Controlled Aliphatic C–H Oxidation



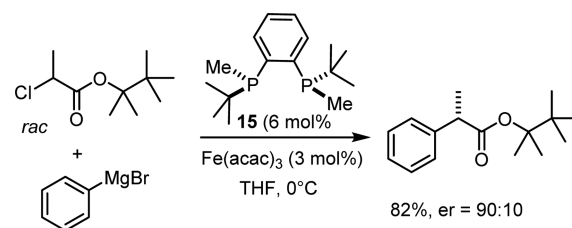
The (directed) functionalization of aromatic and hetero-aromatic C–H groups is arguably no less relevant than the aliphatic C–H hydroxylation referred to above. Although aromatic C–H activation is currently reigned by metals such as Rh, Ir, Ru, and Pd, the number of promising examples using iron or its immediate neighbor elements is rising, even when it comes to C–C bond formation.^{104–109}

■ RADICAL APPROACHES AND TASKS BEYOND REACH OF THE NOBLE COUSINS

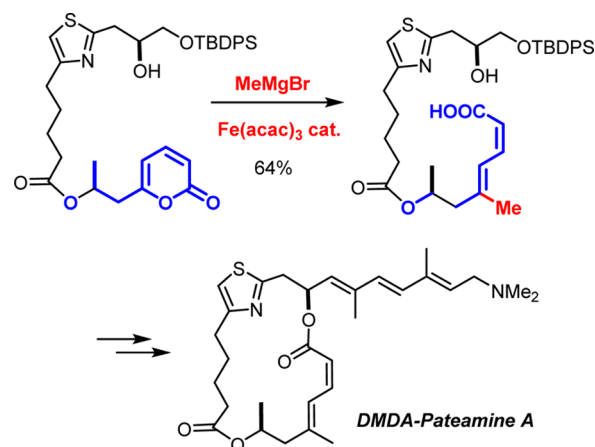
The propensity to engage in odd-numbered redox steps, which need to be suppressed when trying to confer nobility on iron, is the decisive asset in the catalytic C–H functionalization referred to above. It is, perhaps, a misconception or a lack of experience of the community at large that one-electron regimes are often considered less predictable and therefore a less desirable entry point for synthesis and catalysis research. One could even argue that the opposite is true: since they usually lack precedence in the noble metal catalysis arena, iron-triggered radical processes may well serve as gateways to find and establish reactivity pattern that are elusive otherwise.^{110,111}

This notion finds correspondence in a growing body of work on iron-catalyzed cross coupling reactions of arylmagnesium halides with *alkyl* halides (and, more recently, redox-active esters).^{112–118} Even though different mechanisms were conceived, much evidence points to an Fe(II)/Fe(III) manifold. The radical character surfaces in cascades in which a prototype radical 5-*exo*-cyclization precedes the actual coupling step.^{119,120} First asymmetric variants have also been disclosed (Scheme 10).¹²¹ Such transformations are enabling but difficult to accomplish with palladium catalysts;¹²² therefore they illustrate how the scope of cross coupling in general can be extended because the base metal opens an orthogonal reaction channel rather than just duplicating the noble ancestor's behavior. The same is true for nonradical processes, where iron cross coupling also becomes

Scheme 10. Pioneering Study into Iron-Catalyzed Asymmetric Cross Coupling of an Alkyl Halide



Scheme 11. Formal “Cross Coupling” that Engenders Ring Opening of a Heterocycle; Application to the Total Synthesis of a Cytotoxic Macrolide

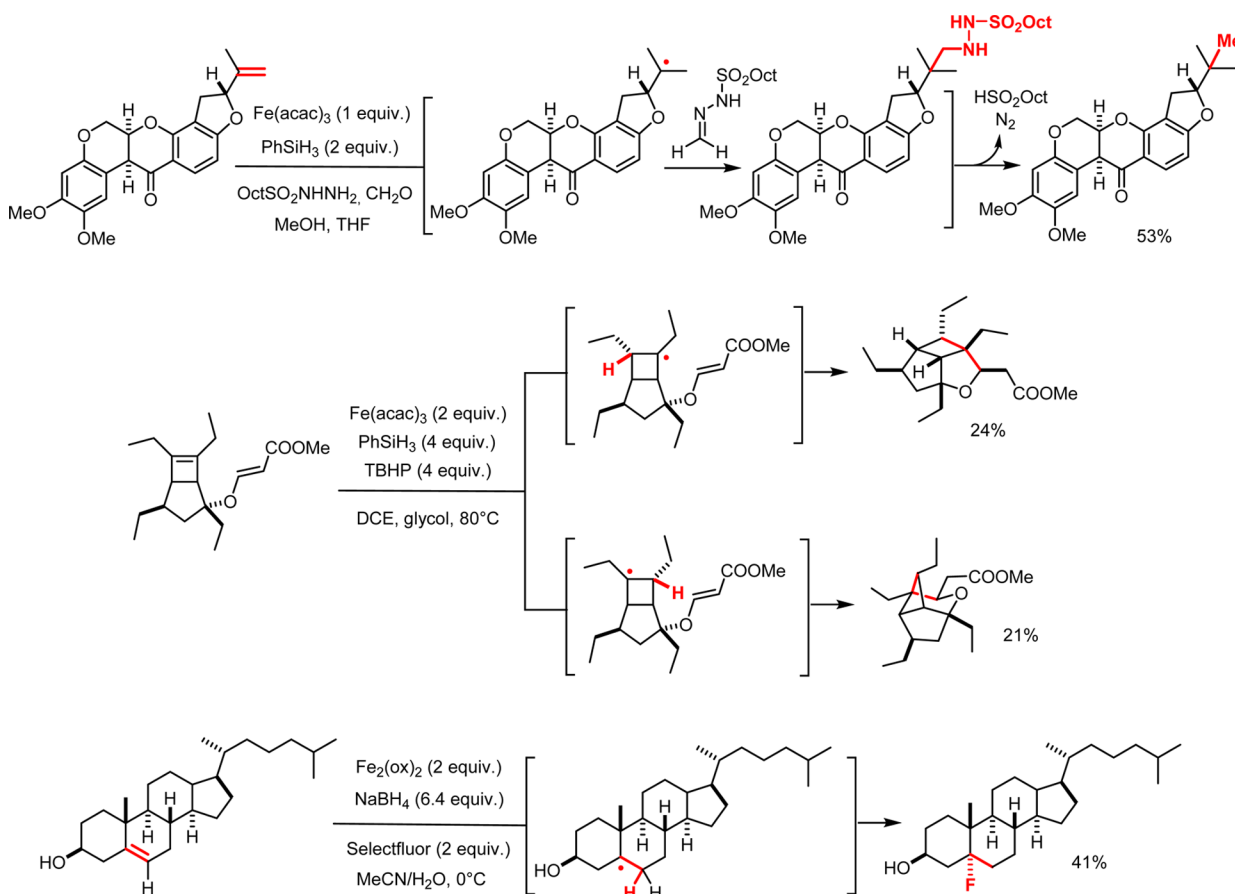


particularly valuable wherever it opens possibilities beyond the canon of palladium chemistry.^{123–128} An instructive case is depicted in Scheme 11.

Such complementarity also speaks for the use of in situ generated iron hydrides as mediators of radical processes, notably for unorthodox functionalizations of alkenes.¹²⁹ The fact that various transition metal hydrides can act as hydrogen atom transfer agents (rather than as hydride or proton donors) is not new,¹³⁰ but the hydrides of iron, cobalt and manganese seem to fare particularly well. The carbon radicals primarily formed on reaction of an intermediate [Fe–H] species with an alkene partner can be engaged in reductive as well as oxidative follow-up chemistry that provides many opportunities for functionalization of sites that are usually difficult to address. The promise of solving previously unmet selectivity issues opens new vistas for retrosynthesis beyond the conventional logic. The selected examples shown in Scheme 12 are representative.^{131–133} Although the yields are sometimes modest and stoichiometric iron is often required at the present stage of development, none of the transformations are straightforward to accomplish otherwise.

In the context of radical chemistry, brief reference has also to be made to the long-known ability of the earth abundant first row transition metals to effect auto-oxidation reactions by formation of high-energy oxygen radical intermediates.¹³⁴ For its aggressiveness, this chemistry was hardly appreciated in a synthetic context. A growing number of examples, however, suggest that even this assessment needs to be revisited, since iron-catalyzed Fenton-type reactions were tamed and used to form various C–C and C–X bonds by dehydrogenative coupling with appreciable selectivity and yield.¹³⁵

Scheme 12. Radical Reactions Mediated by Iron Hydride Species Generated in Situ that Donate H• to an Alkene Partner in the First Place

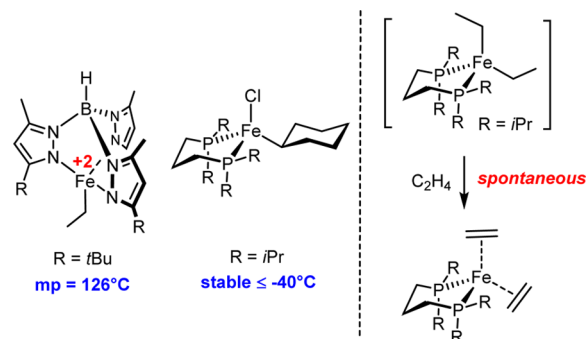


THE ROLE OF SPIN STATE AND SPIN CHANGE

These and many other examples suggest that the somehow pertinacious view that high-spin iron complexes favor unselective organic transformations is improper at best. Even less appreciated is the possibility that high spin iron complexes may actually provide distinct advantages and could be used as enabling vehicles in catalysis.

One possibility of benefiting from a high spin state might consist in the use of singly occupied orbitals to facilitate product dissociation. A priori, a single electron in the proper orbital suffices to foster decomplexation of a ligated product, which, in turn, will accelerate catalyst turnover, if this step is kinetically relevant.

A perhaps more genuine use of high spin states relates to the stabilization of reactive intermediates that would be fleeting otherwise. β -Hydride elimination is an instructive example: this elementary step requires an empty orbital at metal to accept the electrons of the C–H bond to be broken. A high spin iron complex with five or more d-electrons has no such empty orbital and therefore gains stability against this decomposition pathway (Scheme 13). It needs to be restated at this point, however, that orbital energy splitting and hence spin state is potentially geometry-dependent (Scheme 1). Therefore, high spin iron alkyl species endowed with ligand sets that allow for (transient) change in coordination geometry may experience (transient) spin change and hence still succumb to β -hydride elimination; rigid ligand scaffolds, in contrast, should basically switch this elementary step off.^{136,137} This aspect has been analyzed in depth but convincing catalytic arbitrage is still

Scheme 13. Illustration of the Largely Different Stability of Four-Coordinate, High-Spin Fe(II)-alkyl Complexes vis-à-vis β -Hydride Elimination

missing.¹³⁸ Similar arguments can be raised for the binding of a substrate or ancillary ligand to the catalytically active center, which also needs an empty metal orbital to occur and could hence be regulated via spin change. Whereas organometallic iron catalysis is still surprisingly short in examples that make deliberate use of such two-state reactivity, this concept is very well-established elsewhere.^{85,86}

EXOTIC OXIDATION STATES

In a similar vein, the ability of iron to entertain fairly exotic formal oxidation states arguably deserves more careful consideration; the expression “formal” is chosen throughout this Outlook article to emphasize that oxidation states—in contrast

to spin states—are not unambiguous reference points and should be assigned with care. This makes it all the more remarkable that even Fe(VI) complexes have been firmly characterized, although their (catalytic) reactivity awaits detailed study.^{139,140} At the low end, formal Fe(–II), as manifest in Na₂[Fe(CO)₄] (Collman's reagent), is textbook knowledge; it has a rich stoichiometric chemistry that is by no means fully mirrored in catalysis.^{141,142} Interestingly, the isoelectronic d¹⁰-complexes [Fe(C₂H₄)₄][Li(tmeda)]₂ or [Fe(cod)]₂[Li(dme)]₂ obtained upon formal replacement of the CO ligand by kinetically more labile olefins are among the most powerful catalysts for iron cross coupling chemistry known to date.¹²⁰ Although it has been questioned whether formal Fe(–II) plays any role in reactions where the active species is generated in situ from FeX₃ and excess RMgX,⁹⁵ the superb performance of such well-defined complexes is a matter of fact. Other low valent iron complexes such as [CpFe(C₂H₄)₂][Li(tmeda)] (12) (Scheme 6)⁷¹ or [Fe(CO)₃(NO)][Bu₄N] also found promising applications as nucleophilic catalysts.¹⁴³

The recent literature suggests that iron catalysis is potentially capable of covering almost the entire range of organic synthesis.

As mentioned above, the recent literature suggests that iron catalysis is potentially capable of covering almost the entire range of organic synthesis. At the same time, however, it is fair to say that the current status does not necessarily live up to all the possibilities that this element provides; rather, competing methodologies—many of which rely on the use of noble metals—continue to define the state of the art in numerous areas. This gap between the tremendous scope and utilitarian advantages of iron catalysis on the one hand and the status quo on the other hand reflects the many challenges posed by the chemistry of this base metal. The growing awareness of the essential factors that need to be taken into consideration in concert with a steadily refined analytical, spectroscopic, and computational toolbox, however, will entail a rapid transition from mostly empirical knowledge to conceptually and mechanistically well-founded research. In view of its many inherent advantages—not least the promise of a responsible paradigm for chemical synthesis—it is safe to state that research into (homogeneous) iron catalysis is only at the dawn of its development; intellectual incentives and utilitarian recompense are both ahead to reward the brave.

AUTHOR INFORMATION

Corresponding Author

*E-mail: fuerstner@kofo.mpg.de.

Notes

The author declares no competing financial interest.

ACKNOWLEDGMENTS

I sincerely thank all co-workers involved in our iron catalysis project for their excellent experimental work and intellectual contributions. Generous financial support by the Max-Planck-Gesellschaft, the Fonds der Chemischen Industrie, and the Alexander-von-Humboldt Foundation is gratefully acknowledged.

REFERENCES

- (1) Ertl, G.; Knözinger, H.; Schüth, F.; Weitkamp, J., Eds. *Handbook of Heterogeneous Catalysis*, 2nd ed.; Wiley-VCH: Weinheim, 2008; Vol. 1–8.
- (2) Bauer, I.; Knölker, H.-J. Iron Catalysis in Organic Synthesis. *Chem. Rev.* **2015**, *115*, 3170–3387.
- (3) Bolm, C.; Legros, J.; Le Pailh, J.; Zani, L. Iron-catalyzed Reactions in Organic Synthesis. *Chem. Rev.* **2004**, *104*, 6217–6254.
- (4) Plietker, B., Ed. *Iron Catalysis. Fundamentals and Applications*; Springer: Heidelberg, 2011; Top. Organomet. Chem., Vol. 33.
- (5) Bauer, E. B., Ed. *Iron Catalysis II*; Springer International Publishing: Cham, CH, 2015; Top. Organomet. Chem., Vol. 50.
- (6) Bullock, R. M., Ed. *Catalysis without Precious Metals*. Wiley-VCH: Weinheim, 2010.
- (7) Marek, I.; Rappoport, Z., Eds. *The Chemistry of Organoiron Compounds*; Wiley: Chichester, 2014.
- (8) The fact that iron is an essential nutrient does not mean that it is nontoxic; for the lack of an active excretion mechanism, an overload of iron may harm the human body by triggering oxidative stress; for a critical assessment of the intuitive “greenness” of different metals used in catalysis, see: Egorova, K. S.; Ananikov, V. P. Which Metals are Green for Catalysis? Comparison of the Toxicities of Ni, Cu, Fe, Pd, Pt, Rh, and Au Salts. *Angew. Chem., Int. Ed.* **2016**, *55*, 12150–12162.
- (9) European Medicines Agency, Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents, EMEA/CHMP/SWP/4446/2000, London, February 21, 2008.
- (10) For an instructive recent case, see: Ludwig, J. R.; Zimmerman, P. M.; Gianino, J. B.; Schindler, C. S. Iron(III)-catalysed carbonyl-olefin metathesis. *Nature* **2016**, *533*, 374–379.
- (11) Bertini, I.; Gray, H. B.; Lippard, S. J.; Valentine, J. S., Eds. *Bioinorganic Chemistry*; University Science Books: Mill Valley, CA, 1994.
- (12) Fürstner, A. Base-Metal Catalysis Marries Utilitarian Aspects with Academic Fascination. *Adv. Synth. Catal.* **2016**, *358*, 2362–2363.
- (13) For a personal selection of recent highlights, see refs 14, 15, and the following: Okamura, M.; Kondo, M.; Kuga, R.; Kurashige, Y.; Yanai, T.; Hayami, S.; Praneeth, V. K. K.; Yoshida, M.; Yoneda, K.; Kawata, S.; Masaoka, S. A pentanuclear iron catalyst designed for water oxidation. *Nature* **2016**, *530*, 465–468.
- (14) Lee, Y.; Mankad, N. P.; Peters, J. C. Triggering N₂ uptake via redox-induced expulsion of coordinated NH₃ and N₂ silylation at trigonal bipyramidal iron. *Nat. Chem.* **2010**, *2*, 558–565.
- (15) Gärtner, F.; Sundararaju, B.; Surkus, A.-E.; Boddien, A.; Loges, B.; Junge, H.; Dixneuf, P. H.; Beller, M. Light-Driven Hydrogen Generation: Efficient Iron-Based Water Reduction Catalysts. *Angew. Chem., Int. Ed.* **2009**, *48*, 9962–9965.
- (16) The expression “noble” metal remains popular, perhaps for its cultural connotations, even though it is not overly meaningful in the context of homogeneous catalysis. Strictly speaking, it refers to resistance to oxidation, as expressed in the electrochemical redox potential. Note however that many catalytic cycles involving “noble” metals rely exactly on their ability to entertain efficient redox cycles; the Pd(0)/Pd(II) couple as the basis of all canonical cross coupling is representative.
- (17) Hartwig, J. *Organotransition Metal Chemistry. From Bonding to Catalysis*; University Science Books: Mill Valley, CA, 2010.
- (18) Nakamura, E.; Sato, K. Managing the scarcity of the chemical elements. *Nat. Mater.* **2011**, *10*, 158–161.
- (19) Behr, A.; Neubert, P. *Applied Homogeneous Catalysis*; Wiley-VCH: Weinheim, 2012.
- (20) Of course, many exceptions are known; a conceptually interesting case is the field of photoredox catalysis, where noble metal complexes are deliberately used as single-electron reductants/oxidants; for a leading review, see the following and literature cited therein: Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898–6926.
- (21) Ziegler polymerization using early transition metal catalysts is arguably the most important exception.

(22) Proutiere, F.; Aufero, M.; Schoenebeck, F. Reactivity and Stability of Dinuclear Pd(I) Complexes: Studies on the Active Catalytic Species, Insights into Precatalyst Activation and Deactivation, and Application in Highly Selective Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2012**, *134*, 606–612.

(23) Powers, D. C.; Ritter, T. Bimetallic Redox Synergy in Oxidative Palladium Catalysis. *Acc. Chem. Res.* **2012**, *45*, 840–850.

(24) Latin proverb and wordplay: literally it means that that something has to be taken “with a grain of salt”; since the Latin word “sal”, however, also means esprit, insight, prudence, power of judgment, etc., the statement itself should not be taken literally but with some discretion.

(25) Gade, L. H. *Koordinationschemie*; Wiley-VCH: Weinheim, 1998.

(26) Lubitz, W.; Ogata, H.; Rüdiger, O.; Reijerse, E. Hydrogenases. *Chem. Rev.* **2014**, *114*, 4081–4148.

(27) Holland, P. L. Electronic Structure and Reactivity of Three-Coordinate Iron Complexes. *Acc. Chem. Res.* **2008**, *41*, 905–914.

(28) Chirik, P. J.; Wieghardt, K. Radical Ligands Confer Nobility on Base-Metal Catalysts. *Science* **2010**, *327*, 794–785.

(29) Blanchard, S.; Derat, E.; Desage-El Murr, M.; Fensterbank, L.; Malacria, M.; Mourès-Mansuy, V. Non-Innocent Ligands: New Opportunities in Iron Catalysis. *Eur. J. Inorg. Chem.* **2012**, *2012*, 376–389.

(30) Bart, S. C.; Chlopek, K.; Bill, E.; Bouwkamp, M. W.; Lobkovsky, E.; Neese, F.; Wieghardt, K.; Chirik, P. J. Electronic Structure of Bis(imino)pyridine Iron Dichloride, Monochloride and Neutral Ligand Complexes: A combined Structural, Spectroscopic, and Computational Study. *J. Am. Chem. Soc.* **2006**, *128*, 13901–13912.

(31) Bouwkamp, M. W.; Bowman, A. C.; Lobkovsky, E.; Chirik, P. J. Iron-Catalyzed $[2\pi+2\pi]$ Cycloadditions of α,ω -Dienes: The Importance of Redox-Active Supporting Ligands. *J. Am. Chem. Soc.* **2006**, *128*, 13340–13341.

(32) Hoyt, J. M.; Sylvester, K. T.; Semproni, S. P.; Chirik, P. J. Synthesis and Electronic Structure of Bis(imino)pyridine Iron Metallacyclic Intermediates in Iron-Catalyzed Cyclization Reactions. *J. Am. Chem. Soc.* **2013**, *135*, 4862–4877.

(33) Chirik, P. J. Iron- and Cobalt-Catalyzed Alkene Hydrogenation: Catalysis with Both Redox-Active and Strong Field Ligands. *Acc. Chem. Res.* **2015**, *48*, 1687–1695.

(34) Hoyt, J. M.; Schmidt, V. A.; Tondreau, A. M.; Chirik, P. J. Iron-catalyzed intermolecular $[2+2]$ cycloadditions of unactivated alkenes. *Science* **2015**, *349*, 960–963.

(35) For some instructive recent examples, see refs 36–38 and the following: Du, X.; Zhang, Y.; Peng, D.; Huang, Z. Base-Metal-Catalyzed Regiodivergent Alkene Hydrosilylation. *Angew. Chem., Int. Ed.* **2016**, *55*, 6671–6675.

(36) Bleith, T.; Wadepohl, H.; Gade, L. H. Iron Achieves Noble Metal Reactivity and Selectivity: Highly Reactive and Enantioselective Iron Complexes as Catalysts in the Hydrosilylation of Ketones. *J. Am. Chem. Soc.* **2015**, *137*, 2456–2459.

(37) Zhang, L.; Peng, D.; Leng, X.; Huang, Z. Iron-Catalyzed, Atom-Economical, Chemo- and Regioselective Alkene Hydroboration with Pinacolborane. *Angew. Chem., Int. Ed.* **2013**, *52*, 3676–3680.

(38) Inagaki, T.; Ito, A.; Ito, J.; Nishiyama, H. Asymmetric Iron-Catalyzed Hydrosilane Reduction of Ketones: Effect of Zinc Metal upon the Absolute Configuration. *Angew. Chem., Int. Ed.* **2010**, *49*, 9384–9387.

(39) Small, B. L. Discovery and Development of Pyridine-bis(imine) and Related Catalysts for Olefin Polymerization and Oligomerization. *Acc. Chem. Res.* **2015**, *48*, 2599–2611.

(40) McNeill, E.; Ritter, T. 1,4-Functionalization of 1,3-Dienes With Low-Valent Iron Catalysts. *Acc. Chem. Res.* **2015**, *48*, 2330–2343.

(41) Wang, C. X.; Wan, B. S. Recent advances in the iron-catalyzed cycloaddition reactions. *Chin. Sci. Bull.* **2012**, *57*, 2338–2351.

(42) Lane, T. K.; D'Souza, B. R.; Louie, J. Iron-Catalyzed Formation of 2-Aminopyridines from Dienes and Cyanamides. *J. Org. Chem.* **2012**, *77*, 7555–7563.

(43) This entails fairly high kinetic stability of iron carbonyls which hinders their use as catalysts in carbonylation reactions; for progress,

see: Driller, K. M.; Klein, H.; Jackstell, R.; Beller, M. Iron-Catalyzed Carbonylation: Selective and Efficient Synthesis of Succinimides. *Angew. Chem., Int. Ed.* **2009**, *48*, 6041–6044.

(44) For an instructive recent example of the use of isonitriles, see: Bigler, R.; Huber, R.; Mezzetti, A. Highly Enantioselective Transfer Hydrogenation of Ketones with Chiral $(\text{NH})_2\text{P}_2$ Macrocyclic Iron(II) Complexes. *Angew. Chem., Int. Ed.* **2015**, *54*, 5171–5174.

(45) Langer, R.; Leitus, G.; Ben-David, Y.; Milstein, D. Efficient Hydrogenation of Ketones Catalyzed by an Iron Pincer Complex. *Angew. Chem., Int. Ed.* **2011**, *50*, 2120–2124.

(46) Knölker, H.-J.; Baum, E.; Goesmann, H.; Klaus, R. Demetalation of Tricarbonyl(cyclopentadienone)iron Complexes Initiated by a Ligand Exchange Reaction with NaOH—X-Ray Analysis of a Complex with Nearly Square-Planar Coordinated Sodium. *Angew. Chem., Int. Ed.* **1999**, *38*, 2064–2066.

(47) Casey, C. P.; Guan, H. An Efficient and Chemoselective Iron Catalyst for the Hydrogenation of Ketones. *J. Am. Chem. Soc.* **2007**, *129*, 5816–5817.

(48) Quintard, A.; Rodriguez, J. Iron Cyclopentadienone Complexes: Discovery, Properties, and Catalytic Reactivity. *Angew. Chem., Int. Ed.* **2014**, *53*, 4044–4055.

(49) Zhou, S.; Fleischer, S.; Junge, K.; Beller, M. Cooperative Transition-Metal and Chiral Brønsted Acid Catalysis: Enantioselective Hydrogenation of Imines To Form Amines. *Angew. Chem., Int. Ed.* **2011**, *50*, 5120–5124.

(50) Zuo, W.; Lough, A. J.; Li, Y. F.; Morris, R. H. Amine(imine)-diphosphine Iron Catalysts for Asymmetric Transfer Hydrogenation of Ketones and Imines. *Science* **2013**, *342*, 1080–1083.

(51) Pérez-Temprano, M. H.; Casares, J. A.; Espinet, P. Bimetallic Catalysis using Transition and Group 11 Metals: An Emerging Tool for C–C Coupling and Other Reactions. *Chem. - Eur. J.* **2012**, *18*, 1864–1884.

(52) More intricate but conceptually related is the proton-coupled multi-electron reduction of N_2 , which nature performs with the help of iron-rich clusters rather than at a single site; see: Hu, Y.; Ribbe, M. W. Nitrogenases – A Tale of Carbon Atom(s). *Angew. Chem., Int. Ed.* **2016**, *55*, 8216–8226.

(53) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. Iron-Catalyzed Aryl–Aryl Cross-Couplings with Magnesium-Derived Copper Reagents. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654–1658.

(54) Shirakawa, E.; Ikeda, D.; Masui, S.; Yoshida, M.; Hayashi, T. Iron-Copper Cooperative Catalysis in the Reactions of Alkyl Grignard Reagents: Exchange Reaction with Alkenes and Carbometalation of Alkenes. *J. Am. Chem. Soc.* **2012**, *134*, 272–279.

(55) Su, Y.; Jia, W.; Jiao, N. Inexpensive Copper/Iron-Cocatalyzed Reactions. *Synthesis* **2011**, *2011*, 1678–1690.

(56) Handa, S.; Wang, Y.; Gallou, F.; Lipshutz, B. H. Sustainable Fe–ppm Pd nanoparticle catalysis of Suzuki–Miyaura cross-couplings in water. *Science* **2015**, *349*, 1087–1091.

(57) The case of presumably iron catalyzed C–X (X = N, O, S) cross coupling is a caveat, in that only the copper impurities in the chosen precatalyst proved relevant; see: Buchwald, S. L.; Bolm, C. On the Role of Metal Contaminants in Catalyses with FeCl_3 . *Angew. Chem., Int. Ed.* **2009**, *48*, 5586–5587.

(58) Kharasch, M. S.; Fields, E. K. Factors determining the course and mechanisms of Grignard reactions. IV. The effect of metallic halides on the reaction of aryl Grignard reagents and organic halides. *J. Am. Chem. Soc.* **1941**, *63*, 2316–2320.

(59) Percival, W. C.; Wagner, R. B.; Cook, N. C. Grignard reactions. XXI. The synthesis of aliphatic ketones. *J. Am. Chem. Soc.* **1953**, *75*, 3731–3734.

(60) Tamura, M.; Kochi, J. Vinylation of Grignard reagents. Catalysis by iron. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489.

(61) Cahiez, G.; Avedissian, H. Highly stereo- and chemoselective iron-catalyzed alkenylation of organomagnesium compounds. *Synthesis* **1998**, *1998*, 1199–1205.

(62) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. Iron-Catalyzed Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863.

- (63) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. Selective Iron-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Enol Triflates, Acid Chlorides and Dichloroarenes. *J. Org. Chem.* **2004**, *69*, 3943–3949.
- (64) Sherry, B. D.; Fürstner, A. The Promise and Challenge of Iron-Catalyzed Cross Coupling. *Acc. Chem. Res.* **2008**, *41*, 1500–1511.
- (65) Nakamura, E.; Hatakeyama, T.; Ito, S.; Ishizuka, K.; Iles, L.; Nakamura, M. Iron-Catalyzed Cross-Coupling Reactions. *Org. React.* **2014**, *83*, 1–209.
- (66) Mazzacano, T. J.; Mankad, N. P. Base Metal Catalysts for Photochemical C–H Borylation that Utilize Metal–Metal Cooperativity. *J. Am. Chem. Soc.* **2013**, *135*, 17258–15261.
- (67) Karunananda, M. K.; Mankad, N. P. E-Selective Semi-Hydrogenation of Alkynes by Heterobimetallic Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 14598–14601.
- (68) Srimani, D.; Diskin-Posner, Y.; Ben-David, Y.; Milstein, D. Iron Pincer Complex Catalyzed, Environmentally Benign, E-Selective Semi-Hydrogenation of Alkynes. *Angew. Chem., Int. Ed.* **2013**, *52*, 14131–14134.
- (69) Radkowski, K.; Sundararaju, B.; Fürstner, A. A Functional-Group-Tolerant Catalytic *trans* Hydrogenation of Alkynes. *Angew. Chem., Int. Ed.* **2013**, *52*, 355–360.
- (70) Leutzsch, M.; Wolf, L. M.; Gupta, P.; Fuchs, M.; Thiel, W.; Farès, C.; Fürstner, A. Formation of Ruthenium Carbenes by *gem*-Hydrogen Transfer to Internal Alkynes: Implications for Alkyne *trans*-Hydrogenation. *Angew. Chem., Int. Ed.* **2015**, *54*, 12431–12436.
- (71) Fürstner, A.; Majima, K.; Martín, R.; Krause, H.; Kattinig, E.; Goddard, R.; Lehmann, C. W. A Cheap Metal for a “Noble” Task: Preparative and Mechanistic Aspects of Cycloisomerization and Cycloaddition Reactions Catalyzed by Low-Valent Iron Complexes. *J. Am. Chem. Soc.* **2008**, *130*, 1992–2004.
- (72) Lappin, A. G. *Redox Mechanisms in Inorganic Chemistry*; Ellis Horwood Ltd.: Chichester, 1994.
- (73) Groves, J. T.; Myers, R. S. Catalytic Asymmetric Epoxidations with Chiral Iron Porphyrins. *J. Am. Chem. Soc.* **1983**, *105*, 5791–5796.
- (74) Cussó, O.; Ribas, X.; Costas, M. Biologically inspired non-heme iron-catalysts for asymmetric epoxidation; design principles and perspectives. *Chem. Commun.* **2015**, *51*, 14285–14298.
- (75) Legnani, L.; Morandi, B. Direct Catalytic Synthesis of Unprotected 2-Amino-1-Phenylethanols from Alkenes by Using Iron(II) Phthalocyanine. *Angew. Chem., Int. Ed.* **2016**, *55*, 2248–2251.
- (76) Morandi, B.; Carreira, E. M. Iron-Catalyzed Cyclopropanation in 6 M KOH with in Situ Generation of Diazomethane. *Science* **2012**, *335*, 1471–1474.
- (77) Gopalaiah, K. Chiral Iron Catalysts for Asymmetric Synthesis. *Chem. Rev.* **2013**, *113*, 3248–3296.
- (78) Nishikawa, Y.; Yamamoto, H. Iron-Catalyzed Asymmetric Epoxidation of β,β -Disubstituted Enones. *J. Am. Chem. Soc.* **2011**, *133*, 8432–8435.
- (79) Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Xie, J.-H.; Zhou, Q.-L. Enantioselective iron-catalysed O–H bond insertions. *Nat. Chem.* **2010**, *2*, 546–551.
- (80) Zang, C.; Liu, Y.; Xu, Z.-J.; Tse, C.-W.; Guan, X.; Wei, J.; Huang, J.-S.; Che, C.-M. Highly Enantioselective Iron-Catalyzed *cis*-Dihydroxylation of Alkenes with Hydrogen Peroxide Oxidant via an Fe^{III}-OOH Reactive Intermediate. *Angew. Chem., Int. Ed.* **2016**, *55*, 10253–10257.
- (81) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. Challenge toward Structural Complexity Using Asymmetric Catalysis: Target-Oriented Development of Catalytic Enantioselective Diels–Alder Reaction. *Org. Lett.* **2004**, *6*, 4387–4390.
- (82) Jankowska, J.; Paradowska, J.; Rakiel, B.; Mlynarski, J. Iron(II) and Zinc(II) Complexes with Designed *pybox* Ligand for Asymmetric Aqueous Mukaiyama–Aldol Reactions. *J. Org. Chem.* **2007**, *72*, 2228–2231.
- (83) For the catalytic use of a di-coordinate iron amide, see: Yang, J.; Tilley, T. D. Efficient Hydrosilylation of Carbonyl Compounds with the Simple Amide Catalyst [Fe{N(SiMe₃)₂}₂]. *Angew. Chem., Int. Ed.* **2010**, *49*, 10186–10188.
- (84) Ung, G.; Rittle, J.; Soleilhavou, M.; Bertrand, G.; Peters, J. C. Two-Coordinate Fe⁰ and Co⁰ Complexes Supported by Cyclic (alkyl) (amino)carbenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 8427–8431.
- (85) Schröder, D.; Shaik, S.; Schwarz, H. Two-State Reactivity as a New Concept in Organometallic Chemistry. *Acc. Chem. Res.* **2000**, *33*, 139–145.
- (86) Harvey, J. N.; Poli, R.; Smith, K. M. Understanding the reactivity of transition metal complexes involving multiple spin states. *Coord. Chem. Rev.* **2003**, *238–239*, 347–361.
- (87) For an interesting application to mechanistic iron catalysis, see: Takaya, H.; Nakajima, S.; Nakagawa, N.; Isozaki, K.; Iwamoto, T.; Imayoshi, R.; Gower, N. J.; Adak, L.; Hatakeyama, T.; Honma, T.; Takagaki, M.; Sunada, Y.; Nagashima, H.; Hashizume, D.; Takahashi, O.; Nakamura, M. Investigation of Organoiron Catalysis in Kumada–Tamao–Corriu-Type Cross-Coupling Reaction Assisted by Solution-Phase X-ray Absorption Spectroscopy. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 410–418.
- (88) Neese, F. Prediction of molecular properties and molecular spectroscopy with density functional theory: From fundamental theory to exchange-coupling. *Coord. Chem. Rev.* **2009**, *253*, S26–S63.
- (89) Muñoz, S. B., III; Daifuku, S. L.; Brennessel, W. W.; Neidig, M. L. Isolation, Characterization, and Reactivity of Fe₈Me₁₂[−]: Kochi's S = 1/2 Species in Iron-Catalyzed Cross Couplings with MeMgBr and Ferric Salts. *J. Am. Chem. Soc.* **2016**, *138*, 7492–7495.
- (90) Fürstner, A.; Krause, H.; Lehmann, C. W. Unusual Structure and Reactivity of a Homoleptic “Super-Ate” Complex of Iron: Implications for Grignard Additions, Cross-Coupling Reactions, and the Kharasch Deconjugation. *Angew. Chem., Int. Ed.* **2006**, *45*, 440–444.
- (91) Al-Afyouni, M. H.; Fillman, K. L.; Brennessel, W. W.; Neidig, M. L. Isolation and Characterization of a Tetramethyliron(III) Ferrate: An Intermediate in the Reduction Pathway of Ferric Salts with MeMgBr. *J. Am. Chem. Soc.* **2014**, *136*, 15457–15460.
- (92) Bauer, G.; Wodrich, M. D.; Scopelliti, R.; Hu, X. Iron Pincer Complexes as Catalysts and Intermediates in Alkyl–Aryl Kumada Coupling Reactions. *Organometallics* **2015**, *34*, 289–298.
- (93) Parchomyk, T.; Koszinowski, K. Ate Complexes in Iron-Catalyzed Cross-Coupling Reactions. *Chem. - Eur. J.* **2016**, *22*, 15609.
- (94) Daifuku, S. L.; Kneebone, J. L.; Snyder, B. E. R.; Neidig, M. L. Iron(II) Active Species in Iron-Bisphosphine Catalyzed Kumada and Suzuki–Miyaura Cross-Couplings of Phenyl Nucleophiles and Secondary Alkyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 11432–11444.
- (95) Bedford, R. B. How Low Does Iron Go? Chasing the Active Species in Fe-Catalyzed Cross-Coupling Reactions. *Acc. Chem. Res.* **2015**, *48*, 1485–1493.
- (96) Bekhradnia, A.; Norrby, P.-O. New insights into the mechanisms of iron-catalyzed cross-coupling reactions. *Dalton Trans.* **2015**, *44*, 3959–3962.
- (97) White, M. C. Adding Aliphatic C–H Bond Oxidations to Synthesis. *Science* **2012**, *335*, 807–809.
- (98) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. Innate and Guided C–H Functionalization Logic. *Acc. Chem. Res.* **2012**, *45*, 826–839.
- (99) Oloo, W. N.; Que, L., Jr. Hydrocarbon Oxidations Catalyzed by Bio-Inspired Nonheme Iron and Copper Catalysts. In *Comprehensive Inorganic Chemistry II*, 2nd ed.; Reedijk, J.; Poeppelmeier, K., Eds.; Elsevier: Oxford, 2013; Vol 6, pp 763–778.
- (100) Sahu, S.; Goldberg, D. P. Activation of Dioxygen by Iron and Manganese Complexes: A Heme and Nonheme Perspective. *J. Am. Chem. Soc.* **2016**, *138*, 11410–11428.
- (101) Chen, M. S.; White, M. C. A Predictably Selective Aliphatic C–H Oxidation Reaction for Complex Molecule Synthesis. *Science* **2007**, *318*, 783–787.
- (102) Chen, M. S.; White, M. C. Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327*, 566–571.
- (103) Gormisky, P. E.; White, M. C. Catalyst-Controlled Aliphatic C–H Oxidations with a Predictive Model for Site-Selectivity. *J. Am. Chem. Soc.* **2013**, *135*, 14052–14055.

- (104) For pioneering work, see: Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. Iron-Catalyzed Direct Arylation through Directed C–H Activation. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859.
- (105) Nakamura, E.; Yoshikai, N. Low-Valent Iron-Catalyzed C–C Bond Formation—Addition, Substitution, and C–H Bond Activation. *J. Org. Chem.* **2010**, *75*, 6061–6067.
- (106) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Direct C–H Transformation via Iron Catalysis. *Chem. Rev.* **2011**, *111*, 1293–1314.
- (107) Yu, R. P.; Hesk, D.; Rivera, N.; Pelczer, I.; Chirik, P. J. Iron-catalyzed tritiation of pharmaceuticals. *Nature* **2016**, *529*, 195–199.
- (108) Cera, G.; Haven, T.; Ackermann, L. Expedient Iron-Catalyzed C–H Alkylation/Alkylation by Triazole Assistance with Ample Scope. *Angew. Chem., Int. Ed.* **2016**, *55*, 1484–1488.
- (109) Monks, B. M.; Fruchey, E. R.; Cook, S. P. Iron-Catalyzed C(sp²)–H Alkylation of Carboxamides with Primary Electrophiles. *Angew. Chem., Int. Ed.* **2014**, *53*, 11065–11069.
- (110) Studer, A.; Curran, D. Catalysis of Radical Reactions: A Radical Chemistry Perspective. *Angew. Chem., Int. Ed.* **2016**, *55*, 58–102.
- (111) Jahn, U. Radicals in transition metal catalyzed reactions? transition metal catalyzed radical reactions? - a fruitful interplay anyway: part 2. Radical catalysis by group 8 and 9 elements. *Top. Curr. Chem.* **2011**, *320*, 191–322.
- (112) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687.
- (113) Nagano, T.; Hayashi, T. Iron-Catalyzed Grignard Cross-Coupling with Alkyl Halides Possessing β -Hydrogens. *Org. Lett.* **2004**, *6*, 1297–1299.
- (114) Martin, R.; Fürstner, A. Cross-Coupling of Alkyl Halides with Aryl Grignard Reagents Catalyzed by a Low-Valent Iron Complex. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955–3957.
- (115) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. Simple iron-amine catalysts for the cross-coupling of aryl Grignards with alkyl halides bearing β -hydrogens. *Chem. Commun.* **2005**, 4161–4163.
- (116) Czaplak, W. M.; Mayer, M.; Jacobi von Wangelin, A. Domino Iron Catalysis: Direct Aryl–Alkyl Cross-Coupling. *Angew. Chem., Int. Ed.* **2009**, *48*, 607–610.
- (117) Fürstner, A. From Oblivion into the Limelight: Iron (Domino) Catalysis. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364–1367.
- (118) Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S. Redox-Active Esters in Fe-Catalyzed C–C Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 11132–11135.
- (119) Shinokubo, H.; Oshima, K. Transition Metal-Catalyzed Carbon–Carbon Bond Formation with Grignard Reagents – Novel Reactions with a Classic Reagent. *Eur. J. Org. Chem.* **2004**, *2004*, 2081–2091.
- (120) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. Preparation, Structure, and Reactivity of Non-stabilized Organoiron Compounds. Implications for Iron-Catalyzed Cross Coupling Reactions. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787.
- (121) Jin, M.; Adak, L.; Nakamura, M. Iron-Catalyzed Enantioselective Cross-Coupling Reactions of α -Chloroesters with Aryl Grignard Reagents. *J. Am. Chem. Soc.* **2015**, *137*, 7128–7134.
- (122) Nickel is currently the best choice; for leading references see the following and literature cited therein: Schley, N. D.; Fu, G. C. Nickel-Catalyzed Negishi Arylations of Propargylic Bromides: A Mechanistic Investigation. *J. Am. Chem. Soc.* **2014**, *136*, 16588–16593.
- (123) For illustrations of this aspect from this laboratory, see refs 124–127 and the following: Sun, C.-L.; Fürstner, A. Formal Ring Opening/Cross-Coupling Reactions of 2-Pyrone: Iron-Catalyzed Entry into Stereodefined Dienyl Carboxylates. *Angew. Chem., Int. Ed.* **2013**, *52*, 13071–13075.
- (124) Zhuo, C.-X.; Fürstner, A. Concise Synthesis of a Pateamine A Analogue with In Vivo Anticancer Activity Based on an Iron-Catalyzed Pyrone Ring Opening/Cross Coupling. *Angew. Chem., Int. Ed.* **2016**, *55*, 6051–6056.
- (125) Echeverria, P.-G.; Fürstner, A. An Iron-Catalyzed Bond-Making/Bond-Breaking Cascade Merges Cycloisomerization and Cross-Coupling Chemistry. *Angew. Chem., Int. Ed.* **2016**, *55*, 11188–11192.
- (126) Tindall, D. J.; Krause, H.; Fürstner, A. Iron-Catalyzed Cross-Coupling of 1-Alkynylcyclopropyl Tosylates and Related Substrates. *Adv. Synth. Catal.* **2016**, *358*, 2398–2403.
- (127) Fürstner, A.; Méndez, M. Iron-catalyzed Cross-coupling Reactions: Efficient Synthesis of 2,3-Allenol Derivatives. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355–5357.
- (128) Kessler, S. N.; Bäckvall, J. E. Iron-catalyzed Cross-Coupling of Propargyl Carboxylates and Grignard Reagents: Synthesis of Substituted Allenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 3734–3738.
- (129) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912–9000.
- (130) Eisenberg, D. C.; Norton, J. R. Hydrogen-Atom Transfer Reactions of Transition-Metal Hydrides. *Isr. J. Chem.* **1991**, *31*, 55–66.
- (131) Barker, T. J.; Boger, D. L. Fe(III)/NaBH₄-Mediated Free Radical Hydrofluorination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2012**, *134*, 13588–13591.
- (132) Dao, H. T.; Li, C.; Michaudel, Q.; Maxwell, B. D.; Baran, P. S. Hydromethylation of Unactivated Olefins. *J. Am. Chem. Soc.* **2015**, *137*, 8046–8049.
- (133) Ruider, S. A.; Sandmeier, T.; Carreira, E. M. Total Synthesis of (\pm)-Hippolachnin A. *Angew. Chem., Int. Ed.* **2015**, *54*, 2378–2382.
- (134) Fenton, H. J. H. Oxidation of Tartaric Acid in the presence of Iron. *J. Chem. Soc., Trans.* **1894**, *65*, 899–910.
- (135) Itazaki, M.; Nakazawa, H. Iron-Catalyzed Cross-Dehydrogenative-Coupling Reactions. *Top. Organomet. Chem.* **2015**, *50*, 47–81.
- (136) Jové, F. A.; Pariya, C.; Scoblete, M.; Yap, G. P. A.; Theopold, K. H. A Family of Four-Coordinate Iron(II) Complexes Bearing the Sterically Hindered Tris(pyrazolyl)borato Ligand Tp^{tBu,Me}. *Chem. - Eur. J.* **2011**, *17*, 1310–1318.
- (137) Casitas, A.; Krause, H.; Goddard, R.; Fürstner, A. Elementary Steps of Iron Catalysis: Exploiting the Links between Iron Alkyl and Iron Olefin Complexes for their Relevance in C–H Activation and C–C Bond Formation. *Angew. Chem., Int. Ed.* **2015**, *54*, 1521–1526.
- (138) Holland, P. L. Distinctive Reaction Pathways at Base Metals in High-Spin Organometallic Catalysts. *Acc. Chem. Res.* **2015**, *48*, 1696–1702.
- (139) Berry, J. F.; Bill, E.; Bothe, E.; DeBeer George, S.; Mienert, B.; Neese, F.; Wieghardt, K. An Octahedral Coordination Complex of Iron(VI). *Science* **2006**, *312*, 1937–1941.
- (140) Chirik, P. J. An Fe^{VI} Nitride: There Is Plenty of Room at the Top! *Angew. Chem., Int. Ed.* **2006**, *45*, 6956–6959.
- (141) CO and alkenes are π -acceptor ligands; therefore, much of the electron density will reside in the ligand sphere rather than at iron, thus rendering the oxidation state truly a formalism.
- (142) Collman, J. P. Disodium Tetracarbonylferrate—a Transition Metal Analog of a Grignard Reagent. *Acc. Chem. Res.* **1975**, *8*, 342–347.
- (143) Plietker, B.; Dieskau, A. The Reincarnation of the Hieber Anion [Fe(CO)₃(NO)][−] – a New Venue in Nucleophilic Metal Catalysis. *Eur. J. Org. Chem.* **2009**, *2009*, 775–787.