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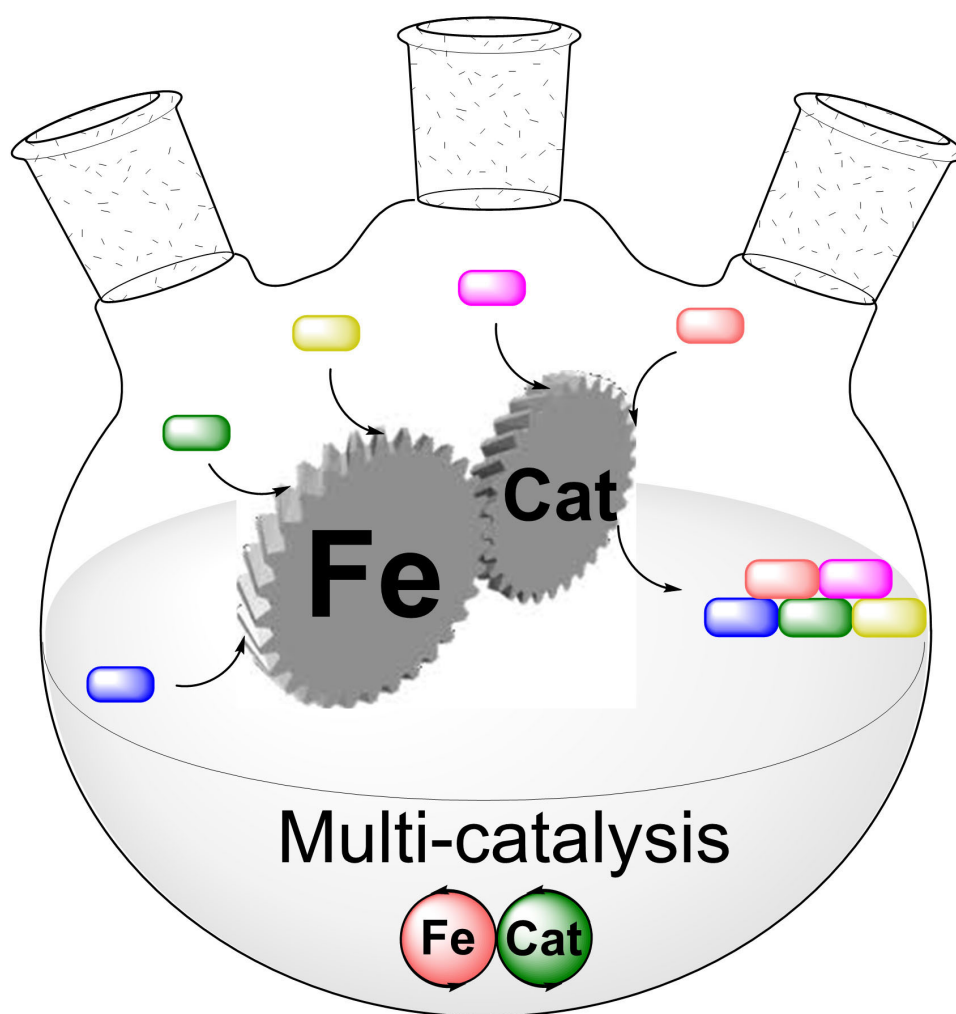
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# Iron-Based Multi-Catalysis: Eco-Compatible Alternative for Complex Molecules Synthesis

Adrien Quintard<sup>\*[a]</sup>



**Abstract:** In the last decade, multi-catalysis has emerged as an excellent alternative to classical methods, rapidly elaborating complex organic molecules while considerably decreasing steps and waste generation. In order to further decrease costs, the application of cheaper and more available iron-based catalysts has recently arisen. Through these iron-based multi-catalytic combinations, greener transformations have been developed that generate complex organic scaffolds

from simple building blocks at lower costs. In addition to the decrease in catalysts costs, it was also demonstrated that in many cases, the application of iron complexes could also lead to unique reactivity features, expanding chemist's available toolbox. All the advantages observed in terms of costs and reactivity, should make iron-based multi-catalysis one of the leading technology of the future.

## 1. Introduction: Iron in Multi-catalysis

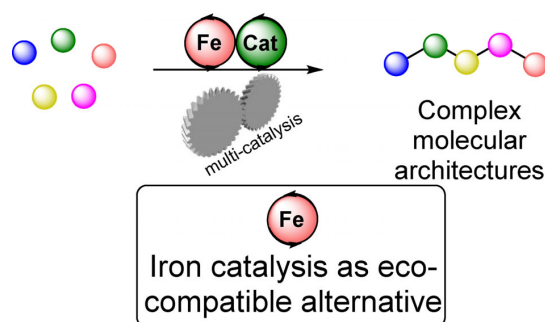
### 1.a Multi-catalysis as an enabling tool

Chemistry is a central science enabling the elaboration of crucial molecular objects necessary for efficient materials, greener energy, or improved drugs. In order to decrease the overall economic and environmental impact during the creation of key organic molecules, chemists must identify new enabling technologies. In this regard, catalysis is able to provide genuine solutions considerably limiting steps or waste generation through unique reagents activation. However, in many cases, use of a single catalyst is insufficient to enable optimal reactivity or selectivity. Nature has for long adopted multiple enzymatic cascades in its complex machinery ensuring the efficiency of elaborated leaving systems. In contrast, chemists have for long relied on the application of a single catalyst and it was only relatively recently that the field of multi-catalysis has been conceptualized and established as a solution for improved organic molecules synthesis.<sup>[1]</sup>

Through the efficient merging of different activation modes, a broad range of building blocks can be efficiently and selectively assembled. As a result, considerable synthetic economies, such as less steps, waste, stoichiometric additives, are obtained resulting in greener elaboration of the above-mentioned key molecular architectures. Most notably, the levels of molecular complexity achievable in one single operation can be considerably increased, a noticeable feature in order to prepare crucial chemical architectures at reduced costs (Scheme 1).

### 1.b Iron as attractive metal alternative

Since more than a decade, multi-catalysis represents a research field in his own. However, as compared to other expensive metals such as rhodium or palladium, it is quite surprising that



**Scheme 1.** Principle of complex molecules synthesis through iron-based multi-catalytic processes.

iron has been under-represented in these transformations. Given its availability (iron is the most abundant metal in the earth's crust after aluminum), most fundamental iron complexes are particularly cheap without any risk over supply.<sup>[2]</sup> Most importantly, the field of iron-catalysis has seen a great boom in the last two decades. As a result, a broad range of efficient iron complexes are available for a multitude of transformations. For example, iron complexes can encompass formal oxidation states ranging from  $-II$  to  $+VI$ .<sup>[2]</sup> In consequence, among potential reactivity, iron catalysts can behave as efficient Lewis acids, engage in single or double electron transfer or as efficient redox active templates. This versatility make them particularly attractive in multi-catalytic transformations where it was recently implemented with great success by the synthetic community.

These pioneering examples demonstrate that complex transformations can be promoted at the same time with higher efficiency and at reduced costs, thanks to the use of appropriate iron-complexes. As a result, when designing a multi-catalytic transformation, instead of focusing exclusively on expensive metals, nowadays, chemist should absolutely test at first potential complementary iron complexes.

It is important to notice from this review that for now, most iron multi-catalytic transformations have relied on the application of relatively simple complexes (mostly  $FeCl_2$ ,  $FeCl_3$ ,  $Fe(acac)_3$ ). This is of course a particularly interesting feature considering the costs of the developed transformations. But it also highlights that improved reactivity and selectivity can be envisaged in the near future through the implementation of more elaborated iron complexes, still keeping in mind that the

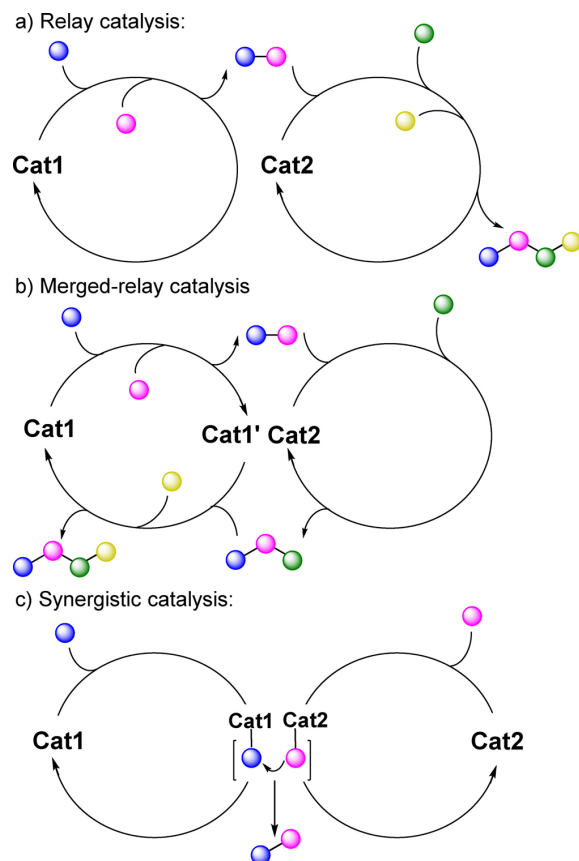
[a] Dr. A. Quintard  
CNRS, Centrale Marseille, iSm2  
Aix Marseille Univ  
Marseille (France)  
E-mail: adrien.quintard@univ-amu.fr

The ORCID identification number(s) for the author(s) of this article can be found under:  
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ligand price should not outcompete the one of the metal. As will be seen along this review, in this context, the application of easily available iron-cyclopentadienone catalysts featuring redox-properties highlight the possibilities offered by the implementation of more elaborated catalysts.

### 1.c Different multi-catalytic approaches

In order for the reader to better understand multi-catalytic principles, the different potential reaction pathways are presented in this section.<sup>[1]</sup> If the two catalysts perform sequentially, the multi-catalytic sequence is called *relay catalysis* (Scheme 2a). The initial catalyst (**Cat1**) triggers through a catalytic cycle the formation of a first intermediate before its reaction in a second distinct catalytic cycle with **Cat2**. In this approach, complex scaffolds are generated at the end of this assembly line in a biomimetic manner, avoiding intermediates isolation. The non-isolation of the intermediates represents one of the major advantages, not only because of the reduced costs associated with the decrease in the number of operations, but also thanks to the unique opportunities to deal with unstable species. If the reaction is performed through the sequential addition of the second catalyst after the first step, the



Scheme 2. Different multi-catalytic pathways.

reaction is called one-pot and will not be presented in this review.<sup>[3]</sup>

If both catalytic cycles are interlocked, a *merged-relay catalysis* is obtained (Scheme 2b). In this relay, **Cat1** can generate a first intermediate directly reacting with the second catalyst, to form another intermediate re-engaging with **Cat2**. In contrast to relay catalysis, in merged-relay catalysis, the overall mechanism can be seen as occurring through a single global catalytic cycle. This type of interlocked catalytic activations, can be found in numerous multi-catalyzed reactions such as typical photoredox multi-catalytic systems.<sup>[4]</sup>

Finally, if two catalysts activate the different reaction components in the same transition state, the reaction is called *synergistic catalysis* (Scheme 2c). This cooperativity between the two catalysts, different from bifunctional catalysis where both catalytic sites are present on the same catalyst, facilitates the formation of the expected product.

It must be pointed out that in some complex reaction settings, the sequence can involve several of these multi-catalytic principles. If a relay sequence is involved prior to a synergistic step, the overall sequence will be described as synergistic.

Within all these multi-catalytic pathways, both the iron complex and the second catalyst can possess multiple roles as will be demonstrated along this review.

### 1.d Aim of the review

The aim of this review is to present the successful examples of homogeneous multi-catalytic transformations employing iron complexes. Focus is done exclusively on reactions where both activating species explicitly act as catalysts. Examples using simple additives (base, counterion...) generating the active catalysts or acting as ligands for the metal center are not covered through this review.<sup>[5]</sup> The multi-catalytic transformations are described according to the catalysts combinations: 1) metal/iron; 2) enzyme/iron; 3) organocatalysis/iron. In order to better understand the different reaction pathways, the type of multi-catalytic principle, the role of the different catalysts

Adrien Quintard discovered chemistry at the technical institute of Castres from University Toulouse III before obtaining a Master degree in 2007 at Lyon (CPE Lyon/University Lyon I). He then moved to Geneva for a PhD obtained in 2011 for his work on metal- and organocatalysis with Prof. Alexandre Alexakis. After a first Postdoc with Prof. Barry Trost at the university of Stanford, he joined Marseille in 2012 for a second Postdoc before obtaining in 2013 an ANR starting grant to initiate a new research program on multi-catalysis. He subsequently joined the CNRS as a senior researcher in 2014 with research interests encompassing a broad range of areas of organic chemistry (catalysis, synthesis, supramolecular chemistry). Recently, his contribution was recognized by the award of the young researcher "Emergence" prize from the Organic Division of the French Chemical Society and he also obtained a Thieme Chemistry Journals award.



and key catalytic elementary steps are discussed in details. When possible, a particular emphasis is made on the role of the iron complex in these transformations

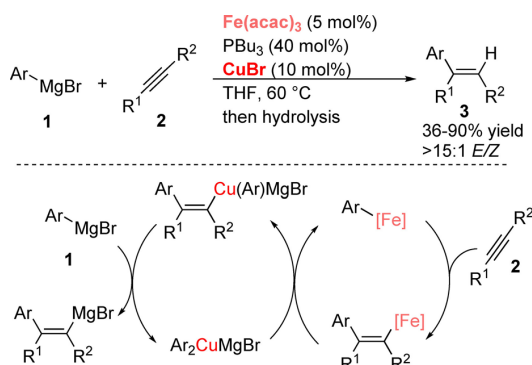
I hope it should help the community identify suitable eco-compatible strategies based on this principle and push chemists to develop their own iron-based multi-catalytic complex organic molecules synthesis. Given the advantages in terms of costs, reactivity and synthetic economies, the application of iron in multi-catalyzed transformations should become a gold standard.

## 2. Metal/Iron Catalysis

### 2.a Organometallic coupling reactions

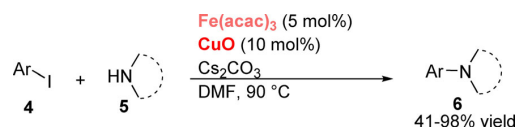
Given the interest of coupling reactions and the prevalence of expensive palladium complexes for such type of transformations, it is not surprising that researchers attempted to develop cheaper alternatives.<sup>[6]</sup> In this section, the most important developments involving cooperative iron-multi-catalysis will be developed. Given the long-known reactivity of copper in cross-couplings, it was first attempted to cross-couple organocopper complexes with iron organometallic complexes. In 2005, the group of Shirakawa and Hayashi reported that Grignard reagents **1** could be coupled with alkynes **2** providing trisubstituted alkenes **3** in good yield (Scheme 3).<sup>[7]</sup> Demonstrating the cost effectiveness of these multi-catalytic processes cheap CuBr and Fe(acac)<sub>3</sub> complexes were applied in this reaction. Transmetalation of the Grignard reagent with the copper salt generates the cuprate, while on the other side the iron complex inserts in the alkyne to form the alkenyl iron complex. Transmetalation of the cuprate with this iron alkenyl organometallic reagent provides the alkenylcuprate, himself transmetalating again with the Grignard reagent. As a result of this synergistic catalytic system, the efficient combination between those two easily available complexes enables transformations otherwise hardly achievable at such costs. In 2009, this approach was extended by the same group to the carbolithiation of alkynes.<sup>[8]</sup>

In 2007, the group of Taillefer extended the highly applied palladium-catalyzed arylation of amines to the use of cheaper



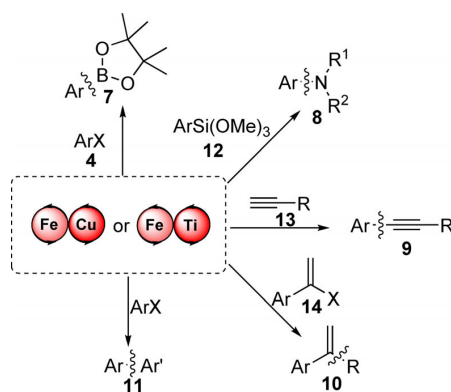
Scheme 3. Synergistic Grignard reagents addition on alkynes.

iron/ copper multi-catalysis (Scheme 4).<sup>[9]</sup> Once again, combining widely available Fe(acac)<sub>3</sub> with CuO, a broad range of aryl-iodides **4** could be cross-coupled with secondary amines **5** in 41 to 98% yield and under relatively mild conditions (90 °C). The reaction pathway is believed to follow the above-mentioned principle of simultaneous activation on each side of both partners by the iron and the copper complexes followed by their transmetalation.



Scheme 4. Synergistic cross-coupling between aryl-iodides and amines.

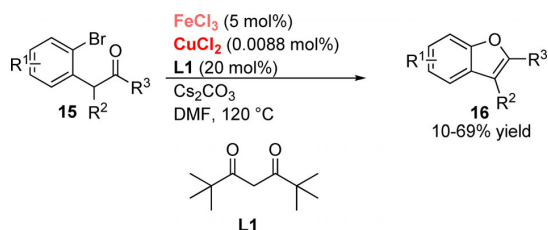
Following these pioneering reports, the principle of copper/ iron multi-catalyzed cross-coupling has been applied with success to numerous other intermolecular couplings (Scheme 5). Demonstrating the power of this approach, it was used in the coupling of amines with aryl-silanes,<sup>[10]</sup> aryl iodides with aryl-amines,<sup>[11]</sup> terminal alkynes with aryl halides,<sup>[12]</sup> aryl bromides with pinacolborane<sup>[13]</sup> or different halides with Grignard reagents (Scheme 5).<sup>[14]</sup> In addition to these iron/copper combination, merging titanium complex with iron also enabled biaryl cross-couplings.<sup>[15]</sup>



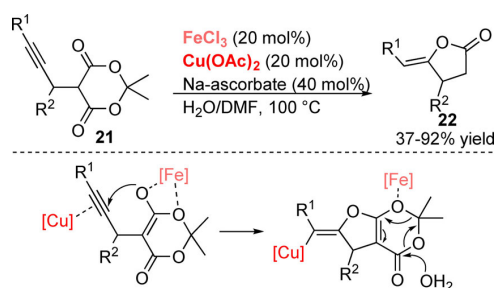
Scheme 5. Synergistic Fe-Cu or Fe-Ti intermolecular cross-coupling reactions.

In complement to these intermolecular couplings, in 2010, the group of Bolm reported that 2-bromobenzyl ketones **15** could be cyclized to benzo[*b*]furans **16** (Scheme 6).<sup>[16]</sup> The enolates generated from the deprotonation of the ketone can couple with the aryl-bromides through the cooperativity between an iron complex and only ppm levels of CuCl<sub>2</sub>. The use of bulky 1,3 diketone **L1** as ligand is crucial in this transformation to stabilize the different metal complexes.

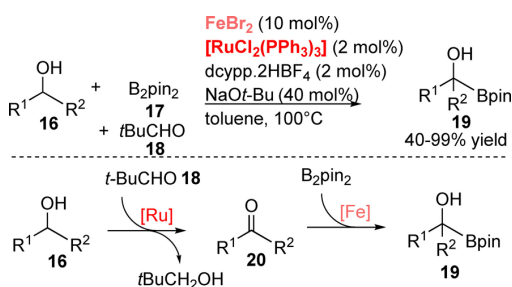
In a last example by the group of Liu, it was shown that multi-catalysis could trigger the addition of pinacol-borane **17** to alcohols **16** (Scheme 7).<sup>[17]</sup> This relay sequence involves a



**Scheme 6.** Synergistic intramolecular cross-coupling between aryl-bromides and enolates.



**Scheme 8.** Synergistic addition of carbonyl derivatives to alkynes.



**Scheme 7.** Relay borane addition to alcohols. dcypp = dicyclohexyl[3-(dicyclohexylphosphino)propyl]phosphine, pin = pinacol.

ruthenium-catalyzed transfer hydrogenation from secondary alcohols to the sacrificial aldehyde oxidant **18**, forming intermediate ketones **20**. These ketones subsequently cross-couple with the boronate through iron catalysis to form the expected tertiary  $\alpha$ -boryl alcohols.

## 2.b Iron for Lewis acidic activation

Beside these couplings reactions possible using other more expensive catalytic systems, the use of iron-catalysis is particularly attractive to discover new type of reactivity as will be demonstrated in the next sections. In most of these examples, numerous fundamental steps can be efficiently combined in a single cascade directly creating complex organic scaffolds. The potential at selectively combining these multiple-steps in cascade represents the great power of multi-catalysis.

Given the Lewis-acidic character of numerous iron complexes ( $\text{FeCl}_3$  for example), it is not surprising that a large number of multi-catalytic sequences have been developed taking advantage of this type of reactivity for electron-rich donors activation. However, given the numerous potential coordination sites in many of these transformations, the mechanisms described in the literature are most of the time only hypothetical. Improvements in most of these transformations will most certainly arise from a determination of these exact mechanisms.

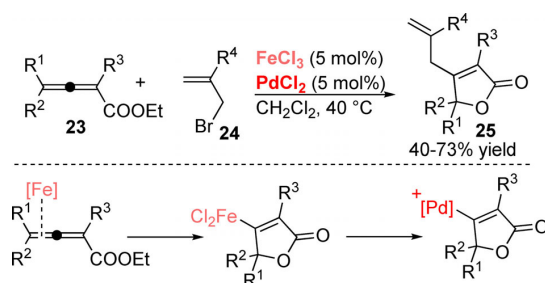
In 2009, the group of Jiao found that mixing two Lewis acids,  $\text{FeCl}_3$  and  $\text{Cu}(\text{OAc})_2$ , synergistic activation of both carbonyl and alkyne functions enabled the cyclization of **21** to  $\gamma$ -alkylidene lactones **22** in 37–92% yield (Scheme 8).<sup>[18]</sup> Starting

from Meldrum's acid derivatives, the iron complex activates the carbonyl group facilitating enolate addition to the copper  $\pi$ -activated alkyne. It was demonstrated that the combination of both Lewis acids was required since using only one of them provided the expected product in less than 12% yield. The use of Na-ascorbate as additive is also necessary to reduce the initial  $\text{Cu}^{\text{II}}$  complex to  $\text{Cu}^{\text{I}}$ .

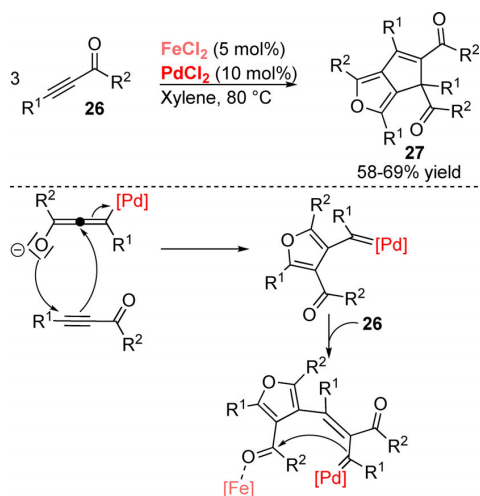
Combining iron and palladium catalysis, Ma and Chen pushed further the complexity in a relay cyclization-allylation (Scheme 9).<sup>[19]</sup> Starting from allenolate **23**, the Lewis acidic  $\text{FeCl}_3$  promotes the cyclization generating an intermediate iron organometallic lactone. Relay transmetalation with the palladium complex followed by a cross-coupling with allyl donor **24**, provides the expected synthetically interesting butenolides **25**. This reaction had previously been developed using gold complexes, however the alternative use of  $\text{FeCl}_3$  considerably decreases the cost of the transformation.<sup>[20]</sup> A next step in terms of eco-compatibility will be to replace the remaining Pd salt with another cheaper catalyst.

In 2012, the group of Jiang used a similar catalysts combination to promote the trimerization of ynones **26** into 4H-cyclopenta[c]furans **27** (Scheme 10).<sup>[21]</sup> In this case, the use of these two simple Lewis acids is supposed to promote a complex relay palladium-catalyzed cycloaddition followed by an iron-catalyzed acyl rearrangement.

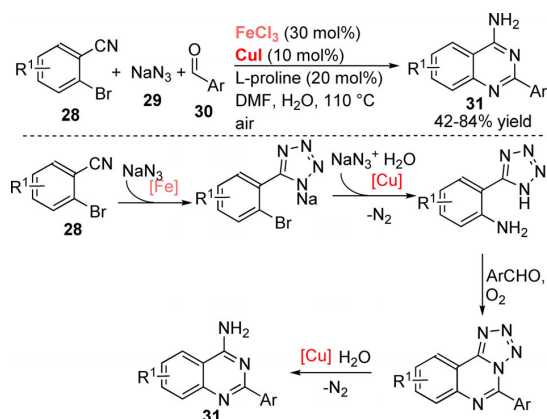
Following this work, Wu and co-workers discovered that combination between  $\text{FeCl}_3$ ,  $\text{CuI}$  and  $L$ -proline as ligand could induce a relay-formation of quinazolin-4-amines **31** (Scheme 11).<sup>[22]</sup> Once again, application of two cheap complexes enables the necessary selective complex relay pathway



**Scheme 9.** Relay formation of butenolides.



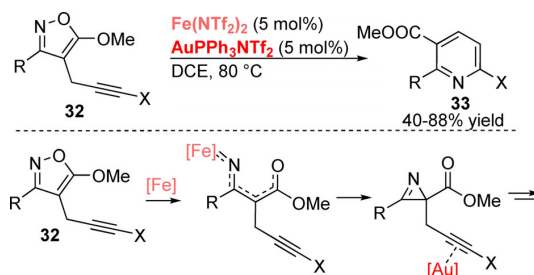
Scheme 10. Relay trimerization of ynones.



Scheme 11. Iron-copper relay quinazoline synthesis.

providing the expected heterocycles in optimal yields. First of all, the iron catalyst is responsible for a cycloaddition between the nitrile **28** and sodium azide through Lewis acidic activation of the nitrile. After this initial tetrazole formation, the copper complex induces a subsequent complex sequence. Initial  $S_NAr$  reaction by a second molecule of sodium azide followed by  $N_2$  release, imine formation and subsequent amine liberation generates the expected quinazoline.

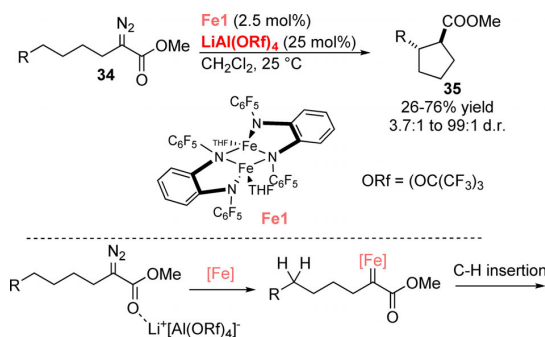
In 2017, Khlebnikov and co-workers disclosed another multi-catalytic application of the Lewis-acidity of iron together with the reactivity of a gold complex (Scheme 12).<sup>[23]</sup> Through this relay sequence, oxazoles **32** possessing alkynes functions on the lateral chain could be rearranged to functionalized pyridines **33**. The Lewis acidic iron complex could coordinate to the starting oxazole inducing its opening and resulting in the formation of a reactive iron-nitrene. Subsequently, the nitrene underwent cyclization forming a strained azirine further reacting with the alkyne activated by the gold carbophilic  $\pi$ -Lewis



Scheme 12. Iron-gold relay pyridine synthesis. Tf = triflate.

acid. In order to avoid the use of expensive gold complex, alternative Lewis acids should also be envisaged.

The electrophilic character of an iron complex **Fe1**, could be combined with the one of a lithium cation to promote a remarkable intramolecular functionalization of alkyl C–H bonds (Scheme 13).<sup>[24]</sup> Starting from a diazo-ester **34**, pre-activation by the Lewis-acidic  $LiAl(ORf)_4$  was necessary to favor the iron-carbene formation. This electron-poor iron-carbene facilitates the challenging C–H insertion, forming interesting cyclopentanes with good levels of diastereoselectivity. Once again, this catalyst combination is crucial in terms of compatibility and reactivity to ensure the optimal overall catalytic sequence. The use of **Fe1** complex possessing a diamine ligand in this transformation demonstrates how simple tuning of the structure of the iron metal center with an easily available ligand can considerably improve the reactivity.



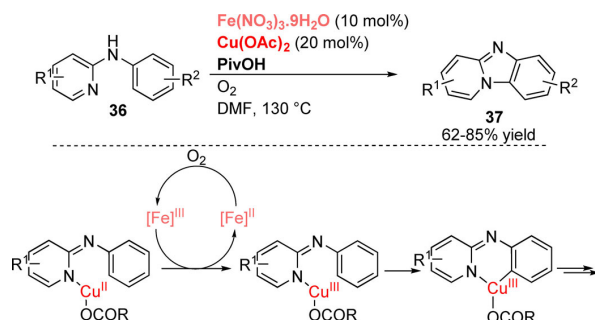
Scheme 13. Iron-lithium synergistic diazo activation for C–H insertion.

## 2.c Iron as redox catalyst

Beside inducing reactions through Lewis-acidic activation, in the last decades, a broad range of iron complexes have been developed to promote complementary redox transformations.<sup>[25]</sup> These reactivities have been subsequently transposed to induce redox changes in complex multi-catalytic settings. For example, iron can be used to promote the re-oxidation of a metal such as copper in a catalytic cycle requiring different oxidation states on the metal.

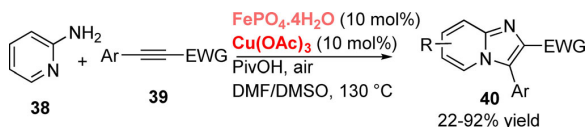
In 2010, the group of Zhu et al. discovered that a  $Cu^{II}$  complex could be oxidized by iron nitrate forming a more electro-

philic Cu<sup>III</sup> intermediate, triggering the subsequent electrophilic aromatic substitution on **36** (Scheme 14).<sup>[26]</sup> After reductive elimination, both Cu<sup>I</sup> and Fe<sup>II</sup> complexes are re-oxidized simply by air to Cu<sup>II</sup> and Fe<sup>III</sup>, starting again the catalytic cycle. Through this synergistic redox pathway, 2-aminopyridines could be readily transformed to pyrido-benzimidazoles **37** simply and cost-effectively.



Scheme 14. Synergistic iron complex oxidizing a Cu<sup>II</sup> complex. Piv = pivaloyl.

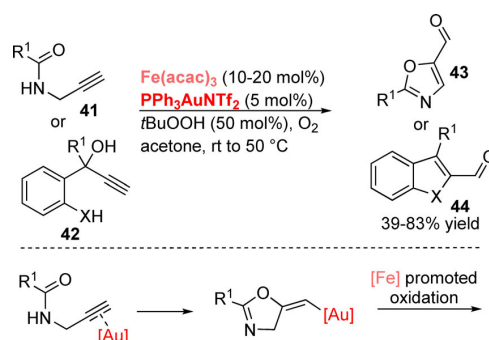
Following this publication, the group of Liu further expanded this principle to the formation of imidazopyridines **40** by the simple condensation of 2-aminopyridines **38** with electron-deficient alkynes **39** (Scheme 15).<sup>[27]</sup> Once again, the copper complex is responsible for the cyclization while the Fe<sup>III</sup> complex re-oxidizes the copper species generated after the cyclization.



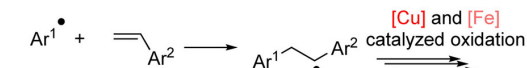
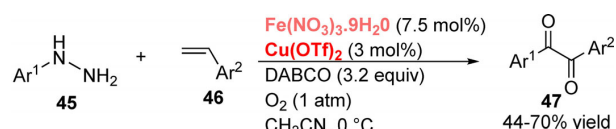
Scheme 15. Synergistic imidazo[1,2-a]pyridine multi-catalytic synthesis.

Beside the re-oxidation of metal centers, iron promoted multi-catalysis can be applied to induce complex oxidation pathways. For example, in 2015, the team of Shi discovered that a gold-catalyzed cyclization could be combined with an iron-promoted oxidation (Scheme 16).<sup>[28]</sup> Through this successful combination, different alkynes **41–42** can be rearranged to oxazoles **43** or indoles **44** in up to 83% yield. The mechanism of the iron-promoted oxidation is unclear but is believed to involve a synergistic Fe-Au catalysis. As a limitation, this process still requires expensive gold complex to trigger the initial alkyne  $\pi$ -activation and cyclization.

In 2013, the group of Jiao discovered that hydrazines **45** could be efficiently coupled with alkenes **46** to create interesting 1,2-diketones **47** (Scheme 17).<sup>[29]</sup> This complex reaction pathway required multiple oxidation events. This goal could be successfully achieved by combining copper and iron complexes in an oxidizing environment. The proposed complex mechanism initially involves oxidation of the hydrazine **45** re-



Scheme 16. Synergistic Au-Fe cyclization-oxidation.



Scheme 17. Relay iron and copper oxidation to 1,2-diketones. DABCO = 1,4-diazabicyclo[2.2.2]octane.

leasing N<sub>2</sub> and forming an aryl radical able to add to the alkene. From the subsequent alkyl radical thus generated, the reaction is believed to occur by multiple oxidation steps promoted both by the copper and the iron complexes.

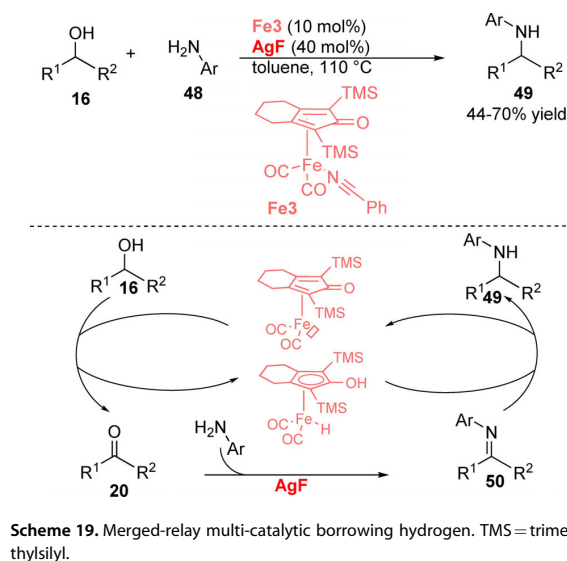
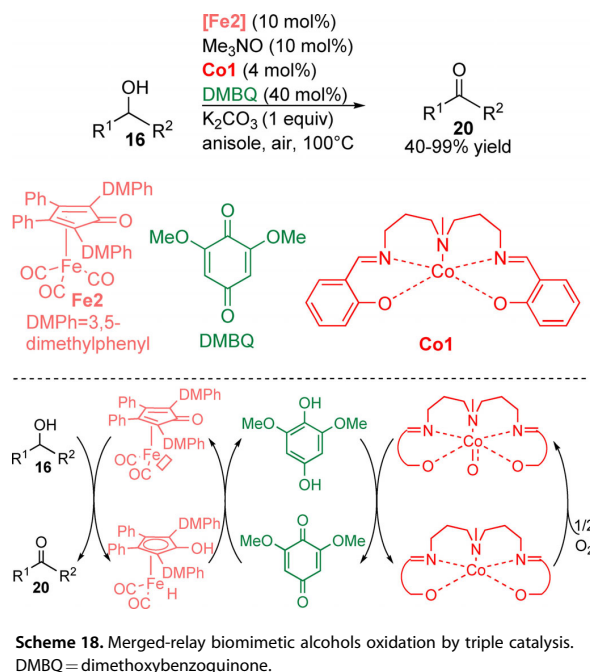
Multi-catalytic systems can also be applied to mimic Nature's NADH complex oxidation machinery. Recently, the group of Bäckvall, demonstrated the full potential of complex multi-catalytic combinations in the biomimetic aerobic oxidation of alcohols **16** to ketones **20** (Scheme 18).<sup>[30]</sup>

This process involves the successful merged-relay assembly of three different catalytic cycles.<sup>[31]</sup> An iron cyclopentadienone complex generated by CO removal from Fe<sup>2</sup>, enables the oxidation of the alcohol to the ketone through hydrogen transfer generating an iron hydride.<sup>[32,33]</sup> This iron hydride subsequently reduces the benzoquinone generating back again the dehydrogenation iron complex. The resulting hydroquinone is re-oxidized by the cobalt complex, itself regenerated by oxidation with air. Through this selective merged-relay cascade, oxygen is efficiently transferred through three easily available catalysts to the alcohol substrate.

Borrowing hydrogen is a good alternative to classical stoichiometric stepwise redox processes.<sup>[34]</sup> In 2013, our group reported that iron-cyclopentadienone complexes could be applied in iron multi-catalyzed borrowing hydrogen allylic alcohols functionalization.<sup>[35]</sup> Based on this approach and later transposition of this reactivity to amines-alkylation with primary alcohols by the group of Feringa,<sup>[36]</sup> the group of Zhao expanded this reactivity to the use of secondary alcohols (Scheme 19).<sup>[37]</sup>

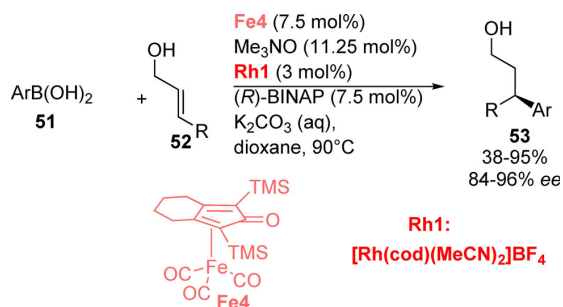
The key to success was the discovery that 40 mol% of AgF could act as a Lewis acid facilitating the imine formation from





the in situ generated ketone. The mechanism of the iron redox pathway is similar to the one of Scheme 18, relying on hydride transfer from the cyclopentadienol complex and dehydrogenation from the cyclopentadienone one. The resulting merged-relay catalysis efficiently transformed a wide variety of secondary alcohols **16** to secondary amines **49**. It must be pointed out that the iron complex used herein is easily available and water and oxygen tolerant, an attractive future concerning the broad applicability of this transformation.

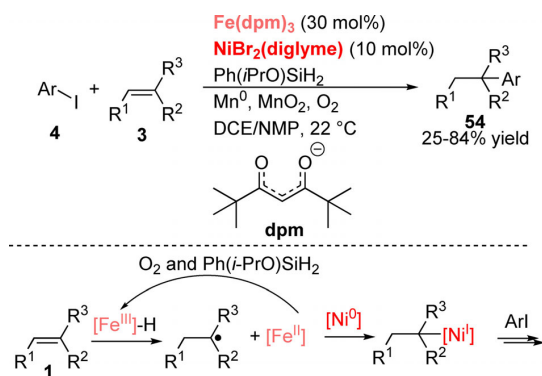
Recently, in 2019, the group of Dydio further applied this iron-catalyzed merged-relay concept to a combination with a chiral rhodium complex (Scheme 20).<sup>[38]</sup> This chiral rhodium catalyst could trigger the enantioselective addition of aryl-boronic acids **51** to the in situ generated  $\alpha,\beta$ -unsaturated aldehydes forming after iron-hydride reduction the final primary alcohols **53** in 84 to 96% ee. In this transformation, the iron complex performs a transient selective redox activation of the organic substrate while the rhodium catalyst is the sole responsible for the enantiocontrol on the final molecule.



**Scheme 20.** Merged-relay iron and rhodium combination in allylic alcohols functionalization. BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, cod = cyclooctadiene.

Selective generation of reactive carbon radicals represents an interesting solution to induce C–C bond formation. In 2018, the group of Shenvi described another type of approach for the addition of aryl-iodides **4** to alkenes **3** (Scheme 21).<sup>[39]</sup>

This transformation implies the combination between Fe(dpm)<sub>3</sub> and a nickel complex. The scope of this reaction, notably generating quaternary centers with good efficiency, is impressively large with more than 60 successful examples of great diversity. The complex multi-catalytic sequence involves generation of an iron-hydride complex reducing the alkyne and forming an alkyl-radical further reacting with a Nickel(0) complex. The active iron(III)-hydride complex is regenerated by oxygen and silicon-hydride. On the other side, the alkyl-nickel

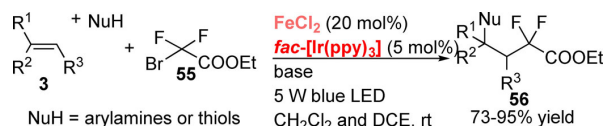


**Scheme 21.** Relay intermolecular addition of aryl-iodides to alkenes. Diglyme = bis(2-methoxyethyl) ether.

species undergoes a classical oxidative addition, reductive-elimination with the aryl-iodide to form the product. Reduction by  $Mn^0$  re-generates the active  $Ni^0$  catalyst.

In order to avoid the numerous stoichiometric additives necessary to perform such catalysts regeneration through multiple redox steps, the group of Cai developed a photoredox system able to add nucleophiles (amine or thiol) and difluoroalkanes **55** to alkenes **3** (Scheme 22).<sup>[40]</sup>

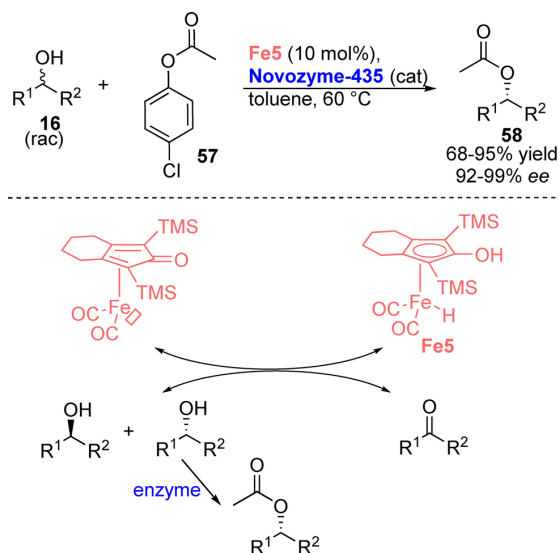
Even-though the mechanism is not clear, it could involve photoredox formation of a difluoroalkane radical adding across the alkene, followed by subsequent trapping with the iron complex and cross-coupling with the nucleophile. In this transformation despite the requirement of an expensive iridium catalyst, three different components are readily assembled under simple conditions and without use of undesired redox additives.



**Scheme 22.** Merged-relay photoredox functionalization of alkenes. Ppy = 2-phenylpyridinato, DCE = 1,2-dichloroethane.

### 3. Enzymatic/Iron Catalysis

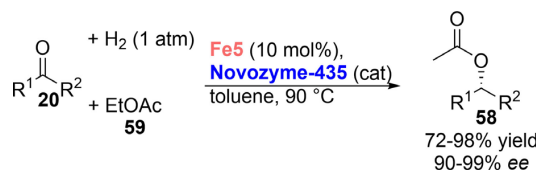
As compared to combination between two metals, multi-catalytic transformations involving iron catalysts and enzymes have been by far less studied despite their great potential. In order to find an alternative to expensive ruthenium complexes in dynamic kinetic resolution (DKR), the group of Rueping applied iron cyclopentadienyl type complex **Fe5** (Scheme 23).<sup>[41]</sup>



**Scheme 23.** Merged-relay iron-enzyme DKR of secondary alcohols.

In combination with Novozyme-435, racemic secondary alcohols **16** could be dynamically resolved to enantioenriched acylated alcohols **58** in up to 99% ee and 95% yield. The mechanism involves interconversion of the two enantiomers of the secondary alcohols through ketone formation by reversible iron-cyclopentadienone complex hydrogen transfer, similar to the one of the borrowing hydrogen previously mentioned. Thanks to the action of the enzyme, only one enantiomer of the alcohol reacts with the acyl donor forming the enantioenriched acylated adduct. The limitation of this system lies in the relative lack of air and moisture stability of **Fe5**. This issue was solved by the group of Bäckvall and later by Zhou and co-workers by modifying the conditions thus enabling the compatible use of alternative bench stable iron-cyclopentadienone complex **Fe4**.<sup>[42]</sup>

In order to complement this methodology to the use of more easily available substrates, the group of Rueping further applied the multi-catalytic combination to a relay hydrogenation of ketones **20**, followed by a DKR on the in situ generated racemic secondary alcohols (Scheme 24).<sup>[43]</sup> In this multi-catalytic reaction, the iron complex possesses a dual role, first to hydrogenate the ketones then to promote the enantiomers interconversion on the resulting racemic alcohols.



**Scheme 24.** Iron-enzyme sequential hydrogenation of ketones merged-relay DKR.

Even-though the developments are still limited, the potential of such approach together with the known reactivity of numerous iron metalloenzymes<sup>[44]</sup> should lead to other iron-enzyme multi-catalytic applications in the near future.

### 4. Organo-/Iron Catalysis

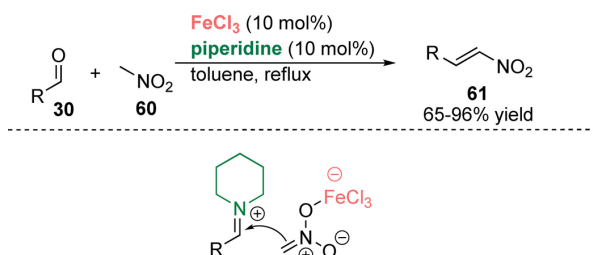
#### 4.a Achiral and racemic reactions

The major advances in multi-catalysis were obtained through the combination between metal- and organo-catalysis. Given the high complementarity between both activation modes, combining them enables to circumvent numerous limitations at using a single catalyst such as reactivity or selectivity issues. Given the impressive developments achieved in this field using classical metal complexes (Pd, Ir, Ru.), it is not surprising that chemists also attempted to take advantage of the reactivity and reduced cost of iron catalysts to develop valuable transformations.

Most notably, given the Lewis acidity of numerous simple iron complexes, they could be efficiently used to enhance the reactivity of various organocatalysts. In this context, different

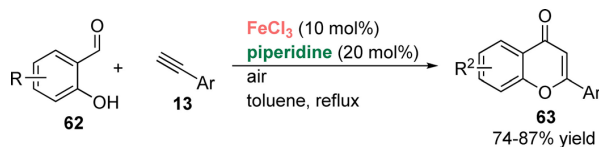
achiral or racemic transformations were successfully developed.

In 2013, the group of Jana illustrated this principle by combining  $\text{FeCl}_3$  with piperidine (Scheme 25).<sup>[45]</sup> This multi-catalytic synergistic system ensures the optimal condensation of aldehydes and nitromethane directly generating nitroolefins **61**. With this simple catalytic combination, the piperidine generates the reactive iminium ion while on the other side,  $\text{FeCl}_3$  activates nitromethane through nitronate formation.



Scheme 25. Synergistic iron-iminium activation.

Based on this principle, in 2011, the group of Maiti used the same simple catalytic combination to promote the condensation of alkynes **13** with hydroxy aromatic aldehydes **62** (Scheme 26).<sup>[46]</sup> Through iminium ion formation, piperidine ensures optimal activation of the aldehyde towards nucleophilic addition of the alkyne. Beside this  $\pi$ -activation of the triple bond,  $\text{FeCl}_3$  is also believed to facilitate aerobic oxidation of the generated alcohol to the flavone.

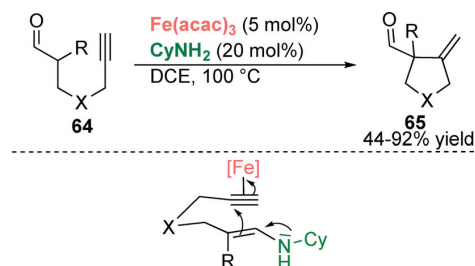


Scheme 26. Synergistic iron-iminium activation for flavones synthesis.

In 2014, Ratovelomanana-Vidal and co-workers discovered that the cyclization of aldehydes to alkenes could be co-catalyzed by  $\text{Fe}(\text{acac})_3$  and a primary amine (Scheme 27).<sup>[47]</sup> This transformation, catalyzed by achiral catalysts creates racemic substituted cyclopentanes **65** through synergistic activation. On one side, the aldehyde is selectively activated by the primary amine catalyst through enamine formation while on the other side the alkyne is activated by the iron complex through Lewis acid activation. In the absence of one of the catalytic component, less than 5% yield is observed, confirming the synergistic role of both catalysts.

It is important to notice that in those transformations, the basic primary or secondary amines catalysts do not inhibit the Lewis acid reactivity of  $\text{FeCl}_3$ .

In the last decade, one of the major advances in organic synthesis came from the successful combination between metal-



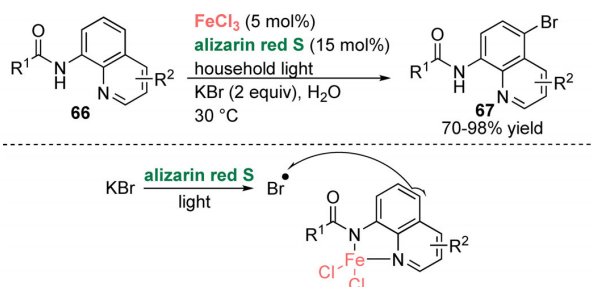
Scheme 27. Synergistic iron-enamine cyclization. Cy = cyclohexyl.

and organo-catalysis in photoredox transformations.<sup>[48]</sup> Unfortunately, once again, many of these transformations rely exclusively on the application of expensive metal complexes. Finding alternatives based on cheaper iron- and organo-catalysts is thus highly desirable.

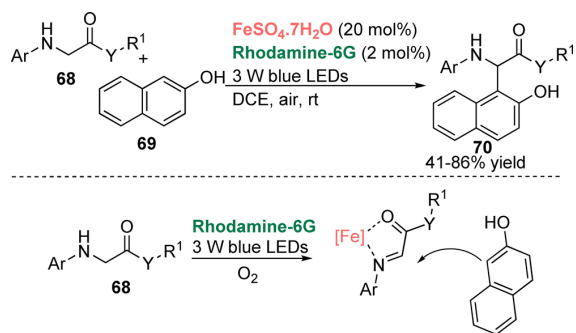
In this context, organic photocatalysts can be combined with Lewis-acid complexes. Mixing alizarin red S as photoredox organocatalyst and  $\text{FeCl}_3$ , selective halogenation of 8-aminoquinoline amides **66** could be performed (Scheme 28).<sup>[49]</sup> The use of this simple Lewis acid enables substrate activation through coordination by both nitrogen atoms. The organic photoredox complex generates a bromine radical adding to the resulting activated quinoline. In addition to the reduced catalysts cost, this relay reaction is performed in water further demonstrating the conditions tolerance of the catalytic system.

In 2018, another relay photoredox reaction was developed by the group of Zhang (Scheme 29).<sup>[50]</sup> This transformation implies photoredox oxidation of a glycine ester **68**. This organo-catalyzed reaction in situ generates a reactive imine, further coordinating to the iron-based Lewis acid. The decreased electron density on this electrophile facilitates the addition of naphthol generating the expected product **70**. Application of an achiral iron complex leads to the formation of a racemic product. Implementation of a chiral Lewis acid should provide opportunities for the development of an enantioselective version of this transformation.

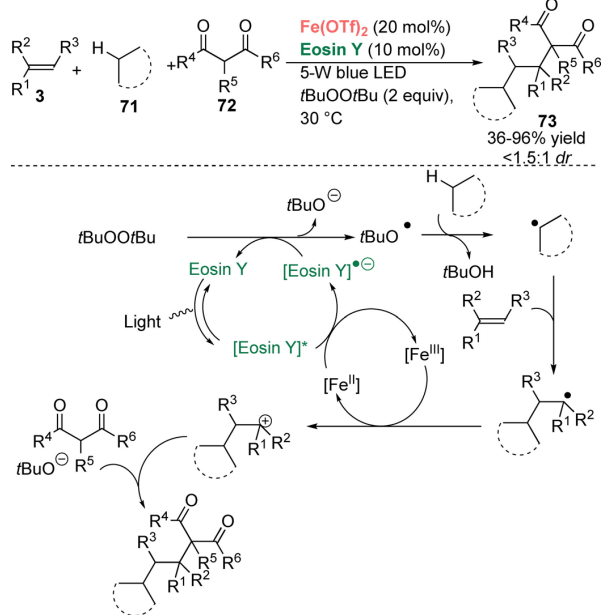
Beside these two examples, more elaborated photoredox transformations have been developed. The group of Song and Li has shown that  $\text{Fe}(\text{OTf})_2$  and Eosin Y could be combined to catalyze the multi-component assembly of alkenes **3**, alkanes **71** and 1,3-dicarbonyl compounds **72** (Scheme 30).<sup>[51]</sup>



Scheme 28. Merged-relay photoredox halogenation of quinolines.



Scheme 29. Photoredox relay oxidation-naphthol addition.



Scheme 30. Photoredox merged-relay racemic cascade.

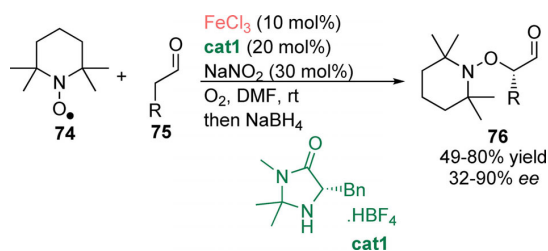
This transformation features a complex merged-relay catalytic sequence. The photoredox organocatalyst ensures formation of the alkyl radical by reacting with the peroxide oxidant while also triggering the oxidation of the iron(II) complex. The generated iron(III) can then react with the formed alkyl radical generating a carbocation, subsequently trapped by the nucleophile. This sequence demonstrates the power of multi-catalysis to trigger complex assembly lines. The only limitation arises from the lack of stereocontrol (dia- and enantio-) which still requires further developments.

#### 4.b Enantioselective reactions by Lewis acid activation

As shown in the above sections, iron-based multi-catalysis is efficient at promoting complex transformations at a reduced cost. However, using combinations of metal complexes, only a

limited number of enantioselective transformations have been developed. The challenge of controlling enantioselectivity requires to master reagents approach in a 3D dimension. Addressing this point constitutes one of the major contribution of multi-catalysis involving iron- and organo-catalysis. It is possible thanks to the ability of both catalysts to improve both reactivity and selectivity during the required transition state but also thanks to their often observed excellent compatibility.

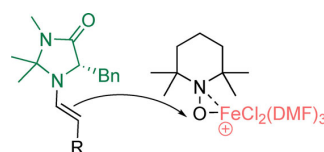
Once again, iron complexes can behave as excellent Lewis acids enhancing reagents electrophilicity. Highlighting this principle, in 2007, Sibi and Hasegawa developed the enantioselective  $\alpha$ -oxyamination of aldehydes **75** (Scheme 31).<sup>[52a]</sup>



Scheme 31. Synergistic enantioselective  $\alpha$ -oxyamination of aldehydes. Bn = benzyl.

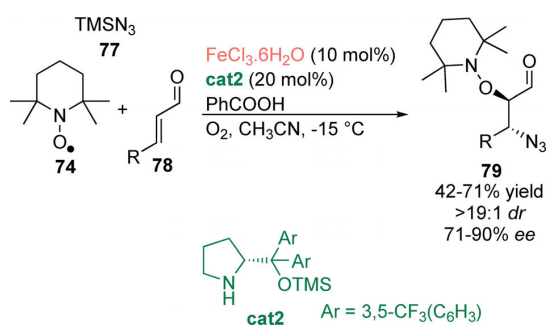
This reaction is highly useful to perform the  $\alpha$ -oxygenation of aldehydes notably if followed by appropriate N–O bond cleavage. Key to success was the successful combination between a chiral secondary amine organocatalyst **cat1** responsible for the enantioselective induction and  $\text{FeCl}_3$ .

It was initially believed that this reaction was ongoing through a radical mechanism. However, in 2010 the group of MacMillan carefully studied the mechanism and found that it was in reality involving a synergistic activation of TEMPO through coordination to the Lewis-acidic iron complex (Scheme 32).<sup>[53]</sup> The electron-rich enamine can thus react with this electrophilic species generating the enantioenriched aldehyde. As a result of this revised mechanism, it was also found that  $\text{NaNO}_2$  was not required to obtain an optimal reactivity.



Scheme 32. Revised mechanism of the synergistic enantioselective  $\alpha$ -oxyamination of aldehydes.

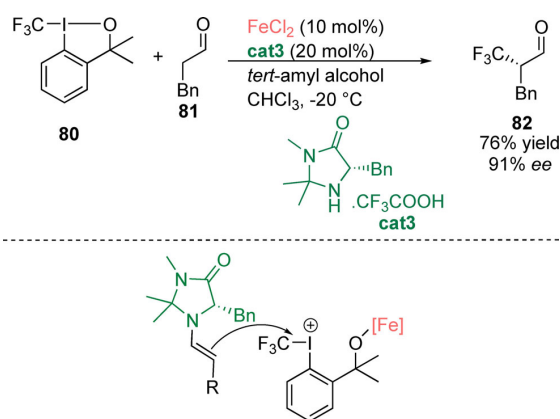
In 2014, this oxyamination was further extended to an additional relay azide addition (Scheme 33).<sup>[54]</sup> This reaction involves the same synergistic multi-catalytic principle with a prior iminium type addition of  $\text{HN}_3$  generated from  $\text{TMSN}_3$  and  $\text{PhCOOH}$ . In this case, the use of diaryl-prolinol silyl ether **cat2** was necessary to catalyze both the 1,4-addition and the enam-



**Scheme 33.** Synergistic enantioselective azidation/ $\alpha$ -oxyamination of aldehydes.

ine functionalization. This strategy represents an interesting alternative for the rapid generation of valuable enantioenriched amino-alcohols.

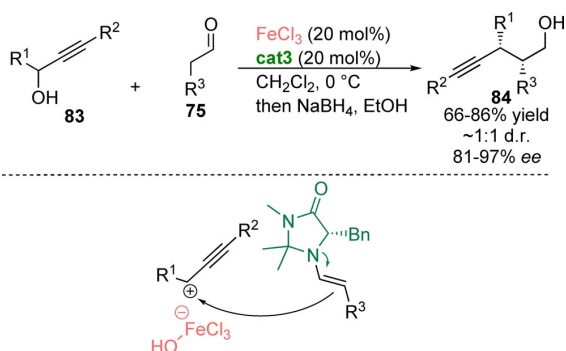
Following this concept of synergistic enamine addition to an iron-activated electrophile, in 2010, the group of MacMillan further expanded the reactivity to the  $\alpha$ -trifluoromethylation of aldehydes (Scheme 34).<sup>[55]</sup>



**Scheme 34.** Synergistic enantioselective  $\alpha$ -trifluoromethylation of aldehydes.

The Lewis acid can activate Togni's reagent **80** towards enantioselective enamine type addition.  $\text{FeCl}_2$  provides key fluorinated aldehyde **82** in 91% ee but the use of  $\text{CuCl}_2$  providing slightly higher enantioselectivity (94% ee) was subsequently preferred.

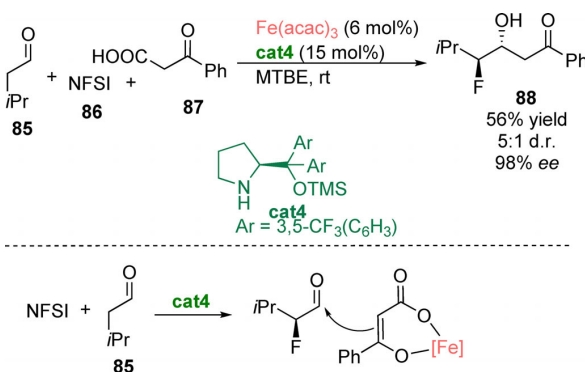
The Lewis acid activation of electrophiles was also applied by the group of Nishibayashi in the alkylation of aldehydes using propargylic alcohols **83** (Scheme 35).<sup>[56]</sup> From the propargylic alcohol,  $\text{FeCl}_3$  triggers the formation of a reactive propargylic cation. Synergistic activation of the aldehyde **75** by the secondary amine catalyst induces the C–C bond formation in excellent enantiocontrol albeit without any diastereocontrol. In the future, the diastereocontrol should be improved by the application of chiral iron complex controlling the stereo-information around the carbocation.



**Scheme 35.** Synergistic enantioselective alkylation of aldehydes.

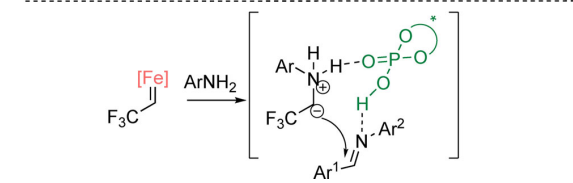
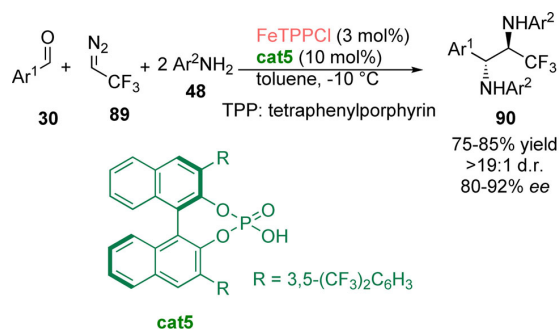
In addition to electrophilic activation, iron complexes have also been applied to activate pro-nucleophiles.

In 2017, my group developed a multi-catalytic multi-component assembly of aldehyde **85**, NFSI and keto-acid **87** (Scheme 36).<sup>[57]</sup> In this relay sequence, the enamine type **cat4** generates a poorly stable enantioenriched fluorinated aldehyde that is directly intercepted by the keto-acid upon activation by the iron complex. As a result of this multi-catalytic combination, enantioenriched fluorohydrin **88** is formed in 98% ee and 5:1 d.r., while replacing the iron complex by a tertiary amine organocatalyst reduced the ee below 72%.



**Scheme 36.** Relay enantioselective multi-catalytic fluorohydrin synthesis. Acac = acetylacetonate, MTBE = methyl *tert*-butyl ether, NFSI = *N*-fluorobenzenesulfonimide.

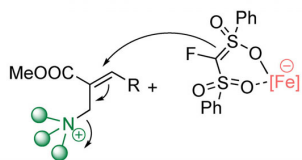
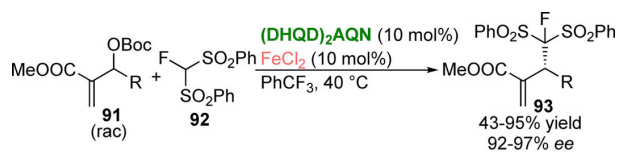
Recently, another relay multi-component diamines synthesis was disclosed by the group of Hu (Scheme 37).<sup>[58]</sup> This interesting multi-catalyzed transformation enables the enantioselective coupling of aldehydes **30**, fluoroalkyl-substituted diazomethane **89** and two equivalents of amines **48**. The relay sequence involves generation of an iron carbene leading to an ylide further adding to the in situ generated imine through phosphoric acid activation. It must be pointed out that the iron complex used here triggers the carbene formation under extremely mild conditions, providing much higher reactivity



Scheme 37. Relay enantioselective multicomponent diamines synthesis.

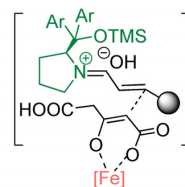
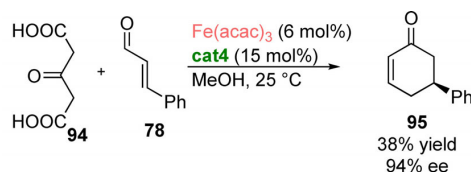
than classical rhodium catalysts. Thanks to the appropriate phosphoric acid catalyst stereocontrol, the final diamines are generated in 80 to 92% ee and almost perfect diastereocontrol (> 19:1 d.r.).

In complement to relay catalysis, in 2011, the group of Shibata reported that fluorinated bis-sulfones **91** could be coupled with Morita-Baylis-Hillman carbonates **92** by a synergistic activation (Scheme 38).<sup>[59]</sup> This transformation could be catalyzed by the quinine derivative (DHQD)<sub>2</sub>AQN alone. However, it was discovered that adding 10 mol% of FeCl<sub>2</sub> considerably improved the enantioselectivity by around 10% ee providing the expected products in **92** to 97% ee. These results could be rationalized by the synergistic activation of both **91** by the tertiary amine organocatalyst and the sulfone **92** by FeCl<sub>2</sub>, contributing to a reactivity enhancement in a better defined transition state.



Scheme 38. Synergistic fluorinated sulfones enantioselective addition. Boc = *tert*-butyloxycarbonyl, (DHQD)<sub>2</sub>AQN = hydroquinidine (anthraquinone-1,4-diyl) diether.

In 2015, Quintard and Rodriguez further reported that combining cheap 1,3-acetonedicarboxylic acid **94** as a 1,3-bis-pro-nucleophile with  $\alpha,\beta$ -unsaturated aldehyde **78** directly provided valuable cyclohexenone **95** in 94% ee (Scheme 39).<sup>[60]</sup> In the absence of the iron complex, the cyclohexenone could be synthesized albeit in a much lower 12% yield and 90% ee, indicating that both aminocatalyst and iron complex work synergistically to enhance the reactivity and the selectivity. This reactivity and selectivity enhancement can be explained by the simultaneous activation of the electrophile by both the aminocatalyst and the pro-nucleophile by the iron complex. Further reaction optimization also revealed that a copper complex could provide slightly higher selectivity in this transformation.



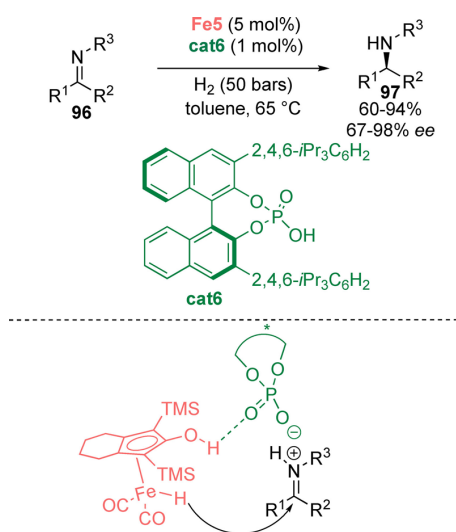
Scheme 39. Synergistic cascade enantioenriched cyclohexenone synthesis.

#### 4.c Enantioselective reactions through iron complex redox properties

As for combinations with other metals or enzymes, the particularly efficient redox changes brought by iron complexes have been used to develop enantioselective complex organo-/ iron-multi-catalytic transformations.

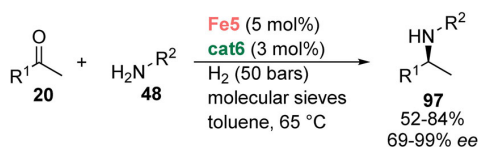
Once again, the unique properties of iron-cyclopentadienyl complexes have been applied with success to this field. In 2011, the group of Beller pioneered the combination of such iron complex together with chiral phosphoric acid organocatalyst **cat6** (Scheme 40).<sup>[61]</sup> This multi-catalytic combination enabled the efficient enantioselective hydrogenation of imine **96** to chiral amines **97** in 67 to 98% ee. The iron complex is able to activate H<sub>2</sub> generating an iron hydride able to add selectively to the imine synergistically activated by the phosphoric acid. Mechanistic experiments also seemed to indicate that the cyclopentadienol unit was simultaneously activated through coordination of the phosphoric acid. Given the lack of enantiocontrol observed using chiral iron cyclopentadienol complexes,<sup>[32]</sup> this multi-catalytic combination provides a smart solution to the challenge associated with enantioselective hydrogenation based on this type of complexes.

Given the interest of this catalytic system, this synergistic reactivity was further expanded by the same group through the in situ generation of the reactive imines (Scheme 41).<sup>[62]</sup>

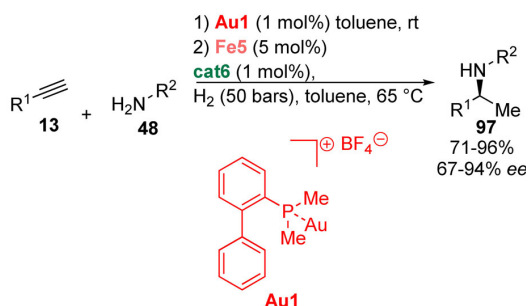


**Scheme 40.** Synergistic iron/phosphoric acid catalysis.

a) Reductive amination of ketones:



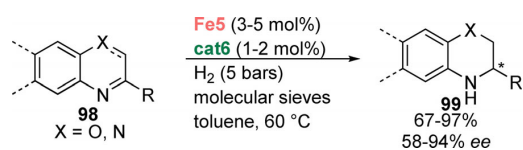
b) Relay hydroamination/ hydrogenation:



**Scheme 41.** In situ imine formation and synergistic hydrogenation.

Starting from mixtures of amines **48** and ketones **20**, imine formation was followed by the synergistic enantioselective iron/phosphoric acid catalytic enantioselective hydrogenation (a). Alternatively, imines could also be in situ generated through a gold-catalyzed hydroamination of alkynes **13** (b). Through this relay sequence, these alkynes could be converted to secondary amines with good levels of enantiocontrol (67–94% ee).

In 2013, the same concept was applied to the hydrogenation of quinoxalines and benzoxazines (Scheme 42).<sup>[63]</sup> The iron-phosphoric acid synergistic catalytic system could induce the hydrogenation of these heterocycles to the corresponding



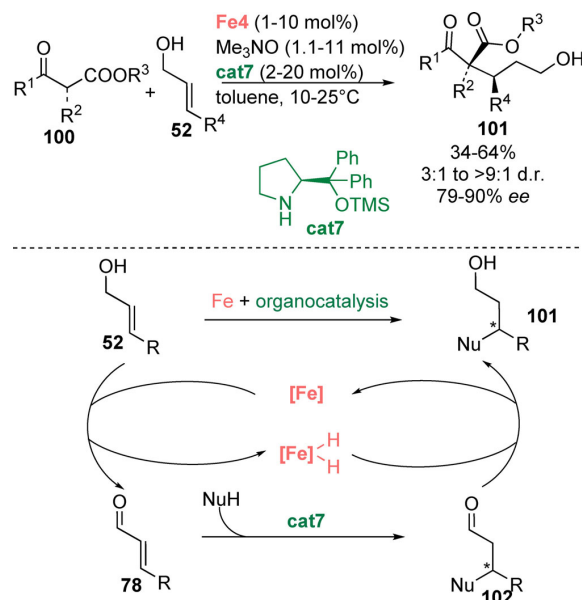
**Scheme 42.** Synergistic iron/phosphoric acid heterocycles hydrogenation.

saturated rings in 58 to 94% ee demonstrating its broad substrate tolerance. It must be pointed out that once again, in situ generation of the quinoxalines from the corresponding di-aldehydes and diamines was possible, further facilitating the formation of the final heterocycles from widely available substrates.

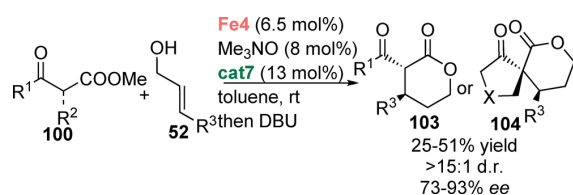
In 2013, Quintard, and Rodriguez pioneered the use of iron cyclopentadienone complexes in borrowing-hydrogen transformations.<sup>[64a]</sup> Applying an iron- organo- multi-catalytic merged-relay, this borrowing hydrogen could be performed enantioselectively forming chiral primary alcohols **101** in 79–90% ee (Scheme 43).<sup>[65]</sup>

This strategy, coupling ketoesters **100** with allylic alcohols **52**, is possible though the merger of both iron cyclopentadienone borrowing hydrogen and amino-catalyzed enantioselective nucleophilic addition on the transient generated aldehyde. Of interest, the iron complex **Fe4** used in this transformation is easily prepared on multi-gram scale and is aerobic and moisture insensitive.

From the obtained alcohols **101**, it was subsequently discovered that a lactonization by alcohol addition to the methyl-esters could be triggered through the one-pot addition of DBU (Scheme 44).<sup>[66]</sup> This relay allylic-alcohols functionalization/ lactonization sequence could generate enantioenriched valuable



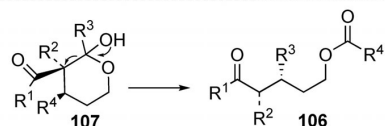
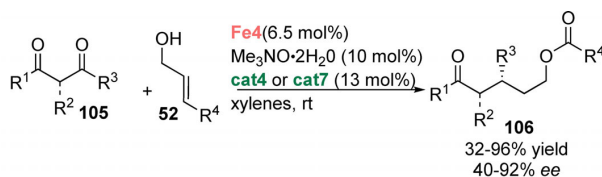
**Scheme 43.** Merged-relay enantioselective borrowing hydrogen.



**Scheme 44.** Merged-relay synthesis of lactones and spirolactones. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

lactones **103** or more challenging spirolactones **104** in one single-pot from commercially available materials.

Of greater synthetic interest, it was later disclosed that starting from diketones **105** instead of ketoesters, further cascade Claisen fragmentation was spontaneously occurring (Scheme 45).<sup>[67]</sup> This multi-catalytic cascade enables the direct assembly of widely available diketones **105** and allylic alcohols **52** into synthetically relevant mono-ketones featuring protected primary alcohols. The synthetic shortcuts provided by this approach were demonstrated in the shortest to date synthesis of different biologically relevant molecules, often reducing the number of required steps by 3 to 6.

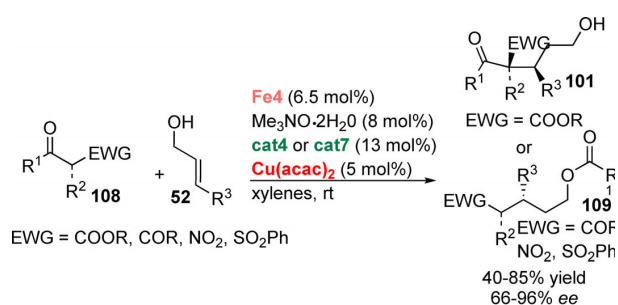


**Scheme 45.** Merged-relay allylic alcohols functionalization/fragmentation.

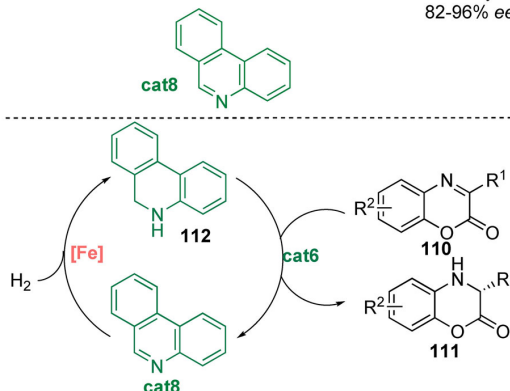
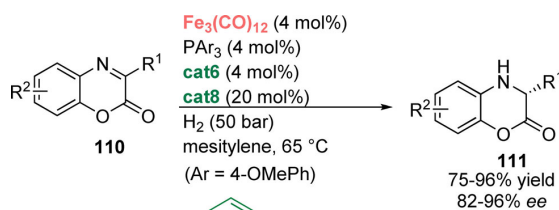
Careful mechanistic study indicated that in order to improve both reactivity and enantioselectivity in these multi-catalytic borrowing-hydrogen processes, incorporation of a third catalyst was necessary (Scheme 46).<sup>[68]</sup> Adding 5 mol% of  $\text{Cu}(\text{acac})_2$  to the above mentioned bi-catalysis increased the enantiocontrol of these transformations by around 10% ee. It was hypothesized that the copper complex coordinates to the pro-nucleophiles enhancing the selectivity of the nucleophilic addition. Furthermore, addition of this copper complex also enabled the application of other classes of pro-nucleophiles such as nitro-esters or sulfones-esters.

Finally, in 2015, in order to find a solution to the efficient enantioselective hydrogenation of benzoxazinones, the group of Beller reported another elegant merged-relay catalysis involving three different catalysts (Scheme 47).<sup>[69]</sup>

This triple catalysis represent a biomimetic NAD(P) type reduction involving chiral phosphoric acid catalyzed hydride transfer from dihydrophenanthridine **112** to the benzoxazi-



**Scheme 46.** Synergistic activation in the triple catalytic borrowing hydrogen.



**Scheme 47.** Merged-relay biomimetic hydrogenation of benzoxazinones by triple catalysis.

ones **110**. In order to recycle the phenanthridine **cat8** formed through this step, an iron complex formed by mixing  $\text{Fe}_3(\text{CO})_{12}$  with a phosphine ligand, selectively hydrogenates it back to dihydrophenanthridine **112**. As a result of this multi-catalytic combination, dihydrophenanthridine transfers hydrogen to the benzoxazinones with excellent enantiocontrol thanks to the phosphoric acid while being continuously regenerated by the iron catalyzed hydrogenation.

Once again, this example demonstrates that combining three catalysts possessing appropriate compatibility and selectivity, complex tasks can be performed with excellent efficiency. In this case, each catalysts perform selectively the assigned



job without interfering with the other steps or reaction constituents and the heterocycles **111** are formed in 82 to 96% ee.

## 5. Conclusions

During a long time, the field of catalysis has been dominated by the use of a single active component, notably metallic complexes. However, in order to ensure optimal reactivity and selectivity, multi-catalytic combinations have emerged as excellent alternatives to these mono-catalytic classical methods. In a last evolution, these multi-catalytic combinations are now becoming more eco-compatible thanks to the application of cheaper and widely available iron catalysts. The combinations between these iron complexes and other catalysts (metals, enzymes or organocatalysts), enable greener transformations directly generating complex organic scaffolds from simple building blocks at lower costs. In addition to the decrease in catalysts costs, it was also demonstrated that in many cases, application of iron complexes can also lead to unique reactivity features.

Given the ongoing progress observed in the design of more powerful iron catalysts, implementation of these complexes of improved reactivity to multi-catalysis should lead to exciting developments. As demonstrated in this review, combining these well-defined complexes in multi-catalytic settings could unlock impressive reactivity.

As a result of the advantages in terms of costs, reactivity and synthetic economies, the application of iron in multi-catalyzed transformations should not be an option but should rather become a gold standard. I hope that this review will push further the community in that direction and that the future will see the next generation of chemists consider iron-based multi-catalytic reactions as classics.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** enantioselective · iron · multi-catalysis · organocatalysis · synthesis

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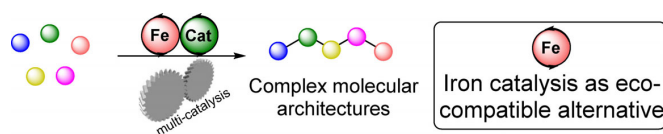
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# Abstract

A. Quintard\*

## Iron-Based Multi-Catalysis: Eco-Compatible Alternative for Complex Molecules Synthesis



**Multi-catalysis** by using cheap and widely available iron complexes represents an excellent solution for the rapid elaboration of complex organic molecules while considerably decreasing steps and waste generation. In addition

to the decrease in catalysts costs, it was also demonstrated that in many cases, the application of iron complexes also lead to unique reactivity features, making iron-based multi-catalysis one of the leading technology of the future.