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Tris(acetylacetonato) Iron(III): Recent Developments and Synthetic Applications

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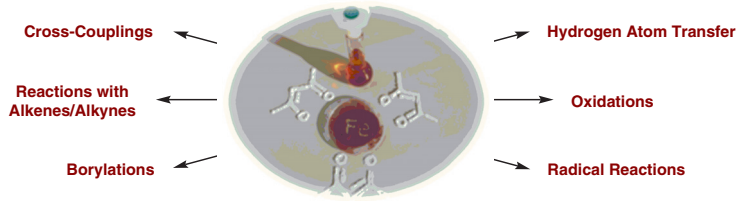

This paper is dedicated to Dr. Holger Butenschön (Leibniz Universität Hannover) on the occasion of his 65th birthday.

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Abstract Tris(acetylacetonato) iron(III) [Fe(acac)$_3$] is an indispensable reagent in synthetic chemistry. Its applications range from hydrogen atom transfer to cross-coupling reactions and to use as a Lewis acid. Consequently, the exceptional utility of Fe(acac)$_3$ has been demonstrated in several total syntheses. This short review summarizes the applications of Fe(acac)$_3$ in methodology and catalysis and highlights its use for the synthesis of medicinally relevant structures and in natural product syntheses.

1 Introduction
2 Hydrogen Atom Transfer (HAT)
3 Oxidations and Radical Transformations
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7 Miscellaneous Reactions
8 Conclusions

Key words Fe(acac)$_3$, tris(acetylacetonato) iron(III), hydrogen atom transfer, radical transformations, cross-couplings, synthetic chemistry, catalysis

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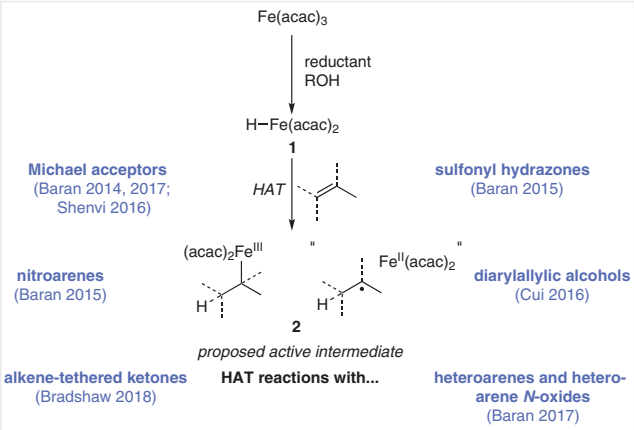
1 Introduction

Being the fourth most abundant element in the Earth's crust, iron possesses various redox properties leading to oxidation states from –II to +VI, with the oxidation states +II and +III being the most favored. The role of iron[1] in synthetic organic chemistry has undergone significant transformation, in particular, its use in homogeneous catalysis has changed the view on iron as a non-noble metal.[2] For decades, the acetylacetonate salt of iron(III), Fe(acac)$_3$, has played a major role in synthetic chemistry. Tris(acetylacetonato) iron(III) is a deep-red crystalline solid with good solubility in alcoholic and chlorinated solvents. Several protocols for the synthesis[3] and purification[3] of Fe(acac)$_3$ are

available in the literature, even videos with practical guidance for laboratory praxis are available on YouTube. Different types of reactions and synthetic procedures have been used and reported over the last decades. The use of $Fe(acac)_3$ in synthetic organic methodology and natural product total synthesis is fairly broad. In this short review, we will focus on the recent contributions in the fields of radical transformations, hydrogen atom transfers from in situ generated iron hydride species, carbometalations and cross-couplings.

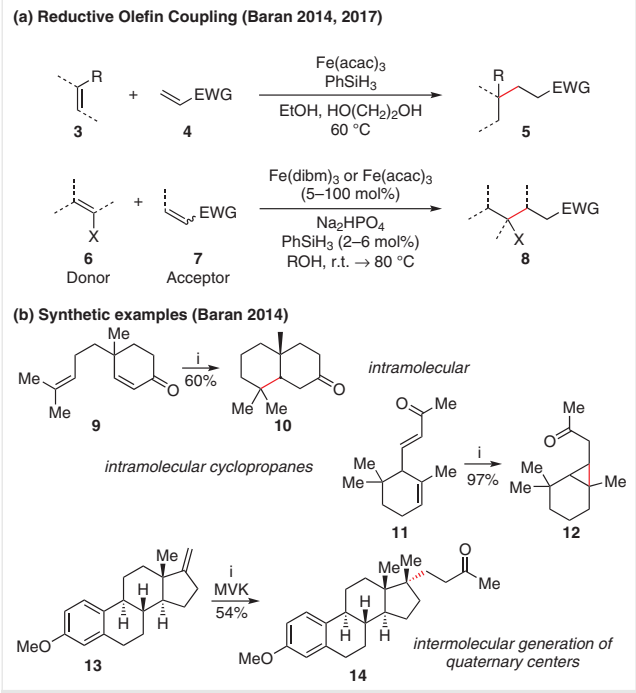
2 Hydrogen Atom Transfer (HAT)

In the recent past, $Fe(acac)_3$ in combination with well-known reducing agents such as silanes has evolved to be an efficient hydrogen atom donor catalyst for the reductive mediation of radical reactions. In 1989, pioneering work on selective functionalizations of electron-rich or non-activated olefins was published by Mukaiyama[4] working on $Co(acac)_2$-catalyzed hydration reactions of non-activated olefins. This class of reactions is based on hydrogen atom transfer (most likely H-atom, no hydride or proton transfer)[5] from transition-metal hydride species **1** to electron-rich olefins, and by so doing, generating the desired reactivity for subsequent transformations (Scheme 1). Up to now, feasible reaction partners for HAT-initiated reactions are olefins, Michael acceptors, nitroarenes, sulfonyl hydrazones, heteroarenes and heteroarene *N*-oxides. Furthermore, radical driven isomerizations and cyclizations of alkene-tethered ketones are reported.



Scheme 1 Overview of HAT-based transformations using $Fe(acac)_3$

In 2014, Baran and co-workers[6] published reductive olefin couplings of electron-rich donor olefins **3** and electron-deficient acceptor olefins **4** (Scheme 2).[6] These types of reactions are based on HATs onto donor olefins **3** to generate radicals of nucleophilic character to add in a 1,4-addition fashion. This addition to acceptor olefins **4** results in the formation of a new carbon–carbon single bond. The reaction pathway for the addition of nucleophilic radicals to electron-withdrawing olefins was studied with numerous model and deuteration experiments. Baran's group deconvoluted the role of all the reagents and reaction parameters revealing the importance of an alcoholic solvent.[6c]

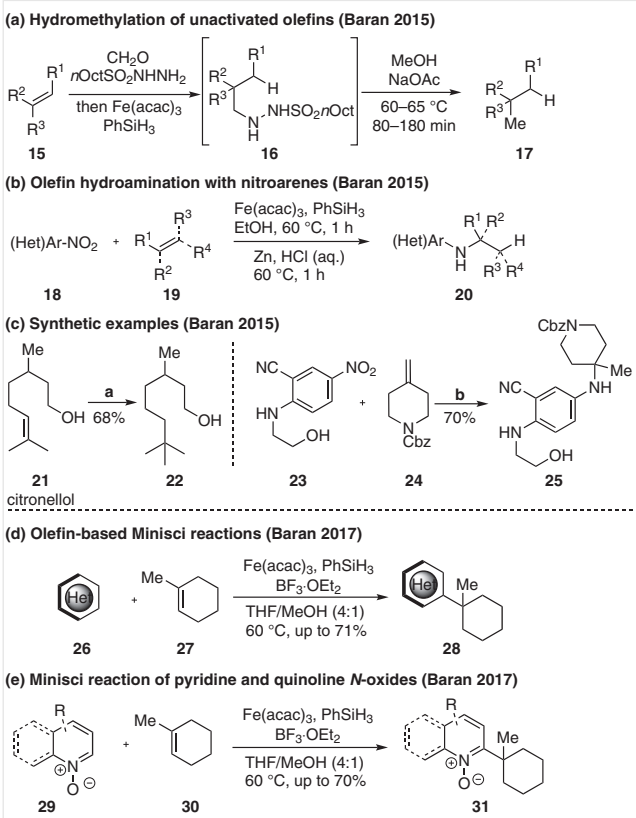


Scheme 2 (a) General scheme for reductive olefin couplings including optimal reaction conditions (EWG: aldehyde, ketone, ester, nitrile, amide, sulfone; X = O, N, S, B, Si, halide), and (b) synthetic examples from the Baran laboratories.[6] (i) $Fe(acac)_3$, $PhSiH_3$, EtOH, $HO(CH_2)_2OH$, 60 °C.

The combination of $Fe(acac)_3$ and phenylsilane in the presence of an alcoholic solvent at elevated temperatures was described by Baran as the optimal combination for such reductive olefin couplings (Scheme 2).[6] These conditions are compatible with numerous functional groups on the donor olefin **6** and tolerate a variety of electron-withdrawing groups on the acceptor **7**.[6] This process has been developed for the synthesis of rosthorin A, which is a kaurane diterpenoid, and its synthesis was split into a cyclization phase (selective C–C bond formations) and an oxidation phase (selective C–O bond formation).[6] This reductive olefin coupling now opens inspiring and fascinating possibilities for disconnections during the cyclization phases.[5,6] The synthesis of decalin **10** was one of the first examples of an intramolecular HAT reaction provided amongst a variety of others in the pivotal paper[6a] published by the Baran group (Scheme 2).[6] Moreover, it has been shown that even cyclopropanes **12** can be obtained in excellent yields using the described transformation.[6a] All in all, one of the major issues of the reductive olefin coupling, besides alkylations, pericyclic reactions, Michael additions, cross-couplings and radical cyclizations, is the powerful potential for generating

all-carbon quaternary centers, which is still a challenging motif in total synthesis. An important example is the generation of quaternary centers at the D-ring of steroids, in particular in proximity to existing quaternary centers (see compound **13**, Scheme 2).[6a] In 2016, Shenvi and co-workers[7] published the use of (*i*PrO)SiPhH$_2$ as an exceptionally mild reductant for metal-catalyzed HATs, which allowed HAT-initiated reactions to be carried out at lower temperatures compared to those used in Baran's protocol.[6,7]

The scope of acceptor molecules was broadened by the use of preformed sulfonyl hydrazones. This protocol now allows the formal incorporation of methyl groups. After radical addition, reductive cleavage of the sulfonyl hydrazine residue leads to the corresponding hydromethylation product **17** (Scheme 3, a).[8] Using this protocol, Baran was able to transform citronellol (**21**) into compound **22** in a single step (Scheme 3, c).[8] Moreover, activity toward the hydroamination of olefins using nitroarenes **18** have been described by the Baran group, with particular dedication to functional group tolerance (Scheme 3, b).[9] A representative example is the synthesis of building block **25**, which is useful for applications in medicinal chemistry (Scheme 3, c).[6c] Furthermore, Minisci reactions of different substituted heteroarenes **26** and olefins **27** show the power and chemoselectivity of these HAT conditions.[6c] In contrast to previously reported HAT conditions,[6] additional Lewis acid activation is required to obtain Minisci products **28** in moderate to good yields (Scheme 3, d).[6c] Among the different Lewis acids tested, BF$_3$ proved to provide the highest yields. In this context, Baran and co-workers described the use of pyridine and quinoline *N*-oxides **29** in combination with additional Lewis acids as being more effective in HAT-based Minisci reactions (Scheme 3, e).[6c]

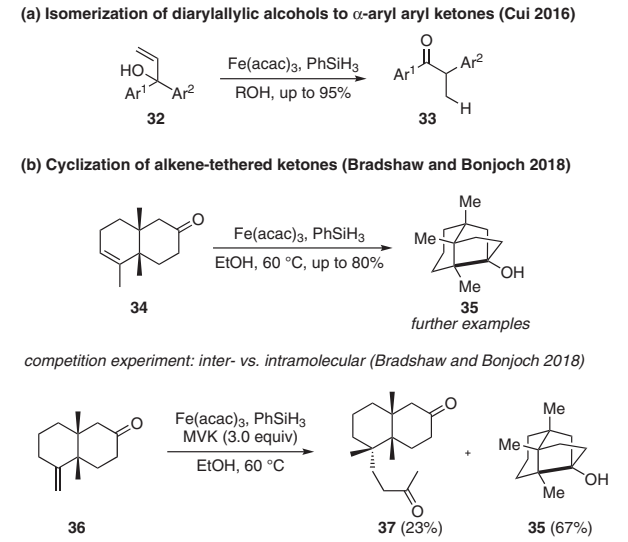


Scheme 3 (a) Hydromethylation,[8] (b) olefin hydroamination using nitroarenes,[9] (c) examples of synthetic relevance,[8,9] (d) olefin-based Minisci reactions,[6c] and (e) Minisci reactions of pyridine and quinoline *N*-oxides[6c] by Baran and co-workers (2015). (i) CH$_2$O, *n*OctSO$_2$NHNH$_2$, then Fe(acac)$_3$, PhSiH$_3$ followed by MeOH, NaOAc, 60 °C, 2 h; (ii) Fe(acac)$_3$, PhSiH$_3$, EtOH, 60 °C, 1 h, then Zn, HCl (aq), 60 °C, 1 h.

The field of HAT-initiated transformations has been broadened in the recent past. In 2016, Cui and co-workers published an iron-triggered isomerization of α,α-diarylallylic alcohols **32** to obtain α-aryl ketones **33** in excellent yields (Scheme 4, a).[10] The reaction proceeds via 1,2-migration of an aryl radical and subsequent single-electron-initiated oxidation. However, the choice of suitable reaction partners for HAT-driven processes is certainly not limited to intramolecular olefins, heteroatom-substituted alkenes, Michael acceptors, heteroarenes, nitroarenes and sulfonyl hydrazones. The intramolecular addition of nucleophilic radicals to carbonyl groups of any kind has been studied extensively over the years.[11] The use of ketones as acceptors in radical reactions is limited due to its reversibility, which is shown in rate studies that provide slower ring closure of nucleophilic radicals to ketones than the corresponding ring opening of alkoxy radical counterparts.[11] This pathway is well-known as the Beckwith–Dowd ring expansion.[11,12] Yet, in 2018, the group of Bonjoch and Bradshaw reported on the intramolecular additions of HAT-obtained radicals onto ketone **34** and provided a number of examples in good to very good yields (e.g., **35**, Scheme 4, b).[12] The radical cyclization of alkene-tethered ketone **34** provides stable tricyclic alcohol **35**. Competition experiments on this reaction pathway in the presence of methyl vinyl ketone show the predominance of the intramolecular cyclization onto the carbonyl group by comparison to the intermolecular reductive olefin coupling with Michael acceptors (Scheme 4, c).[6,12]

In 2015, Pronin and co-workers published an approach for the construction of the tricyclic framework of paxilline indole diterpenes **39**. The key step was a radical-polar crossover polycyclization initiated by Fe(acac)$_3$ and Shenvi's[7] (*i*PrO)SiPhH$_2$, followed by an aldol addition of the in situ formed iron enolate (Scheme 5, a).[13] Furthermore, this strategy was used to obtain intermediate **41** to accomplish the total synthesis of emindole SB (Scheme 5, b).[13]

For the construction of the *trans*-decalin unit **43** of hispidanin A, the Liu group also used Baran's HAT-mediated radical polyene-like cyclization strategy (Scheme 5, c).[14] In

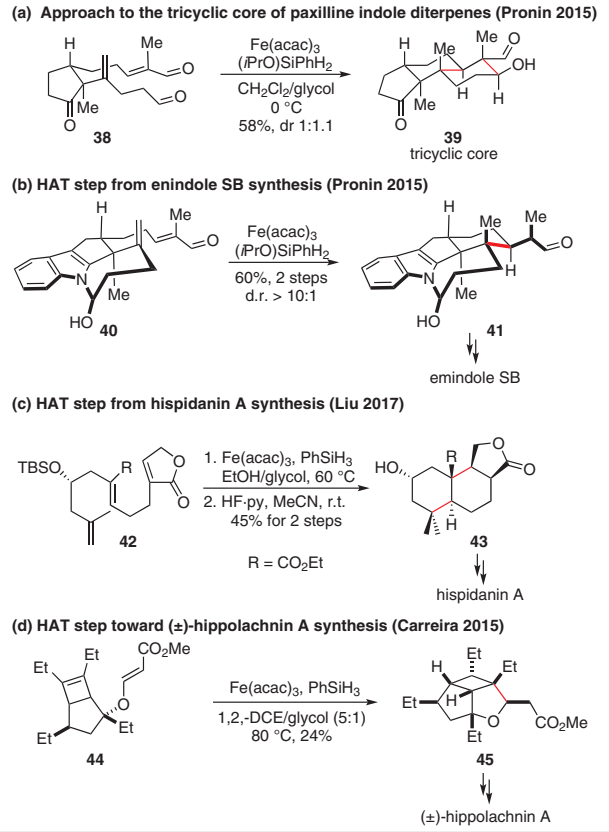


Scheme 4 (a) Cui's[10] protocol for the isomerization of diarylallylic alcohols, and (b) Bradshaw and Bonjoch's[12] radical cyclization of alkene-tethered ketones; MVK = methyl vinyl ketone

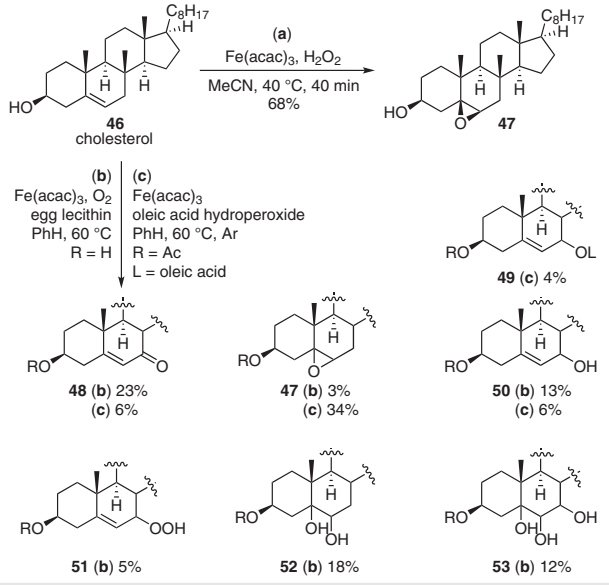
2015, Carreira and co-workers published the HAT-initiated construction of the core of (±)-hippolachnin A **45** using analogous conditions (Scheme 5, d).[6,15]

3 Oxidations and Radical Transformations

In addition to HAT-initiated reactions, $Fe(acac)_3$ appears in different types of radical-driven synthetic transformations. For decades, the combination of $Fe(acac)_3$ and oxidizing agents (such as dioxygen, hydrogen peroxide and organo hydroperoxides) is known to be able to oxidatively functionalize benzylic and allylic positions,[1] as well as aromatic systems and conjugated alkenes.[16–19] From a historical point of view, it is pertinent to mention the first experiments using $Fe(acac)_3$ for the oxidation of cholesterol (**46**) by Kimura and co-workers in 1973 (Scheme 6, a).[16] In combination with hydrogen peroxide, the iron-catalyzed oxidation effected selective β-epoxidation of cholesterol (**46**) in 68% yield. This reaction has been investigated to provide a model reaction for biological oxofunctionalizations of steroid skeletons.[16] Moreover, extensive studies toward biological oxidations of liposomal cholesterol (**46**) have been described by Kimura and co-workers in 1982[19] and in 1983[18] using $Fe(acac)_3$ as the iron catalyst in the presence of either egg lecithin or unsaturated long-chain fatty acids such as oleic acid (Scheme 6). Oxidation mixtures tend to give compositions of various oxidized products **47–53** with overall moderate to decent conversions (Scheme 6, b and c).[18,19]



Scheme 5 (a) Pronin's HAT for the construction of paxilline indole diterpene cores,[13] (b) the synthesis of emindole SB,[13] (c) the HAT step of Liu's hispidanin A synthesis,[14] and (d) construction of the core of (±)-hippolachnin A by Carreira[15]

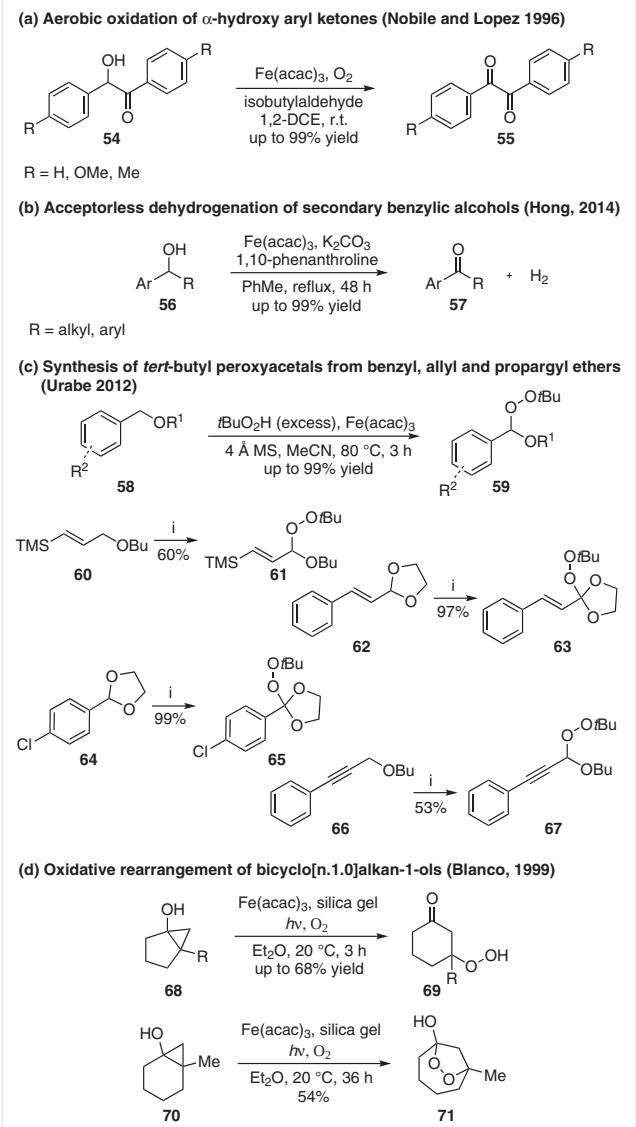


Scheme 6 (a) Historical overview of β-epoxidation of cholesterol by Kimura 1973,[16] and autoxidations of cholesterol (b) by Kimura 1983[18] and (c) in 1982[19]

However, in this work by Kimura,[16] Fe(acac)$_3$ in the presence of oxidizing agents was the origin for further iron-based oxidations in a wide variety of substrates. More recently, several methods for the oxidation of benzylic alcohols and benzylic positions have been published (Scheme 7). In 1996, Nobile, Lopez and co-workers demonstrated the aerobic oxidation of α-hydroxy aryl ketones **54** to obtain symmetrically substituted 1,2-diketones **55** in good to excellent yields using catalytic amounts of Fe(acac)$_3$, dioxygen and a sacrificial aldehyde, albeit the substrate scope was limited to aromatic substituents (Scheme 7, a).[20] Further dehydrogenations with catalytic amounts of Fe(acac)$_3$ in the presence of potassium carbonate and 1,10-phenanthroline to obtain aryl ketones **57** were performed by the Hong group in 2014 (Scheme 7, b).[21] The advantage of this methodology is the absence of sacrificial reagents for hydrogen acceptance. However, the oxidation only proceed with secondary alcohols in benzylic positions (Scheme 7).[21] A similar type of reaction is the introduction of organo peroxides at benzylic, allylic or propargylic ether positions. In 2012, Urabe reported the synthesis of *tert*-butyl peroxyacetals **58** starting from the corresponding ethers **58** by applying Fe(acac)$_3$ in catalytic amounts with an excess of *tert*-butyl hydroperoxide in toluene (Scheme 7, c).[22] The corresponding peroxyacetals **59** (further examples: **61**, **63**, **65**, **67** and others)[22] were obtained in excellent yields. In 1999, Blanco and co-workers described an oxidative rearrangement of bicyclo[n.1.0]alkan-1-ols **68** with a reagent mixture of catalytic amounts of Fe(acac)$_3$, silica gel, and dioxygen under irradiation (100 W domestic light bulb) to obtain the corresponding β-hydroperoxy cyclohexanones **69** in decent yields (Scheme 7, d).[23] By prolonging the reaction time from three to 36 hours, in the case of cyclopropane **70**, a subsequent ring closure yielding the corresponding peroxyacetal **71** was observed (Scheme 7, d).[23]

Furthermore, Pan and co-workers published an alkenylation of cyclic ethers **73** using Fe(acac)$_3$ and DTBP as a radical starter. This reaction proceeds via a radical decarboxylative sp^2–sp^3 coupling and afforded alkenylated dioxanes **74**, pyrans and tetrahydrofurans in good yields (Scheme 8, a).[24] The same group reported the use of cycloalkanes, e.g., cyclopentane, cyclohexane (**76**), cycloheptane etc., for the decarboxylative alkenylation and obtained the corresponding alkenylated cycloalkanes **77** in moderate to very good yields (Scheme 8, b).[25]

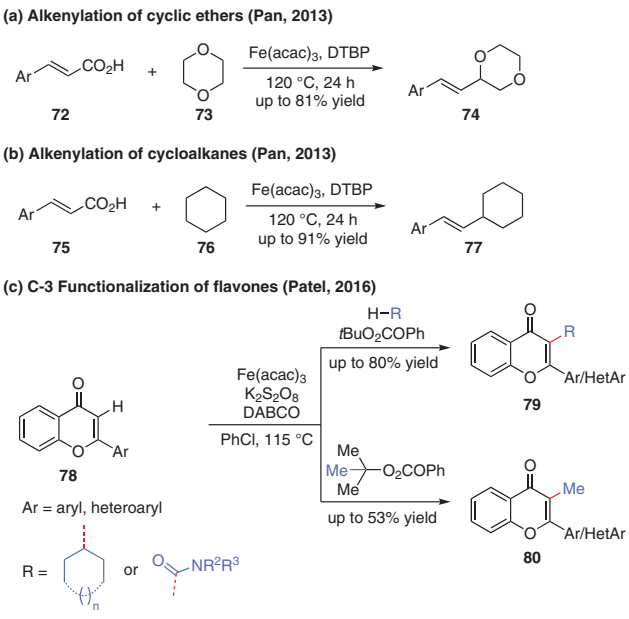
In 2016, Patel and co-workers reported the selective functionalization of the C-3 position in flavones **78** by using catalytic amounts of Fe(acac)$_3$, potassium persulfate, DABCO and either *tert*-butyl peroxybenzoate for the introduction of a single methyl group, or cycloalkynes or formamides for the introduction of a cycloalkyl residue or formyl group at elevated temperatures (Scheme 8, c).[26]



Scheme 7 (a) Aerobic oxidation of α-hydroxy aryl ketones by Nobile and Lopez,[20] (b) dehydrogenation of secondary benzylic alcohols by Hong,[21] (c) synthesis of several *tert*-butyl peroxyacetals by Urabe,[22] and (d) oxidative rearrangement of bicycloalkanols in the presence of oxygen by Blanco.[22] (i) TBHP, Fe(acac)$_3$, 4 Å MS, MeCN, 80 °C, 3 h.

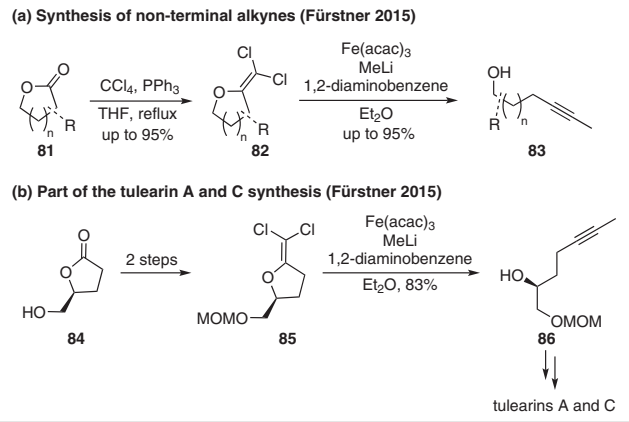
4 Synthesis and Use of Alkynes and Allenes

Numerous applications of iron in the context of alkyne chemistry varying from alkyne synthesis to selective addition and annulations have been published in the recent



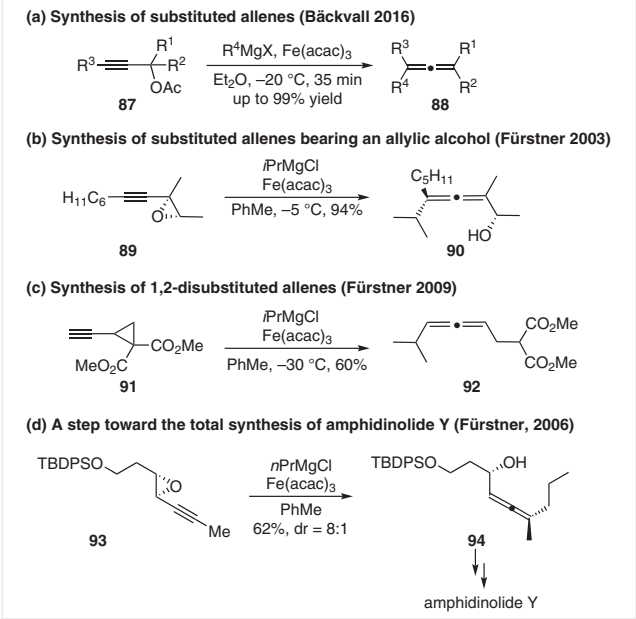
Scheme 8 (a) Alkenylation of cyclic ethers,[24] (b) alkenylation of cycloalkanes by Pan,[25] and (c) peroxide-mediated C-3-functionalization of flavones;[26] DTBP = di-*tert*-butyl peroxide

past.[1,2] In 2015, Fürstner reported a new method for the synthesis of non-terminal alkynes **83** starting from lactones **81** (Scheme 9).[27] The lactone was converted into the corresponding 1,1′-dichloro olefin **82** and subsequently treated with $Fe(acac)_3$ and methyllithium. The method provides a broad scope of methylated alkynes **83** in yields of up to 95% (Scheme 9, a). This strategy was applied to the synthesis of fragment **86** in Fürstner's total synthesis of tulearins A and C (Scheme 9, b).[27]



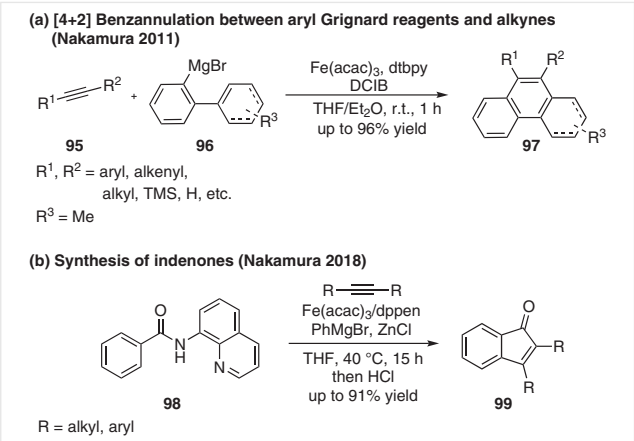
Scheme 9 (a) Fürstner's synthesis of non-terminal alkynes, and (b) application to the synthesis of tulearin[27]

When it comes to the use of alkynes as starting materials, Bäckvall's group published the synthesis of substituted allenes **88** starting from propargylic acetates **87** (Scheme 10, a).[28] Bäckvall and Kessler utilized a large substrate scope obtaining good to excellent yields of the allene products. The reaction proceeds via and an iron-catalyzed cross-coupling mechanism. Earlier, Fürstner introduced examples for the synthesis of substituted allenes **90** starting either from propargylic epoxides **89**[29] or propargylic cyclopropanes **91**[30] bearing a geminal diester on the cyclopropane core (Scheme 10, b and c). A convenient example from natural product total synthesis is Fürstner's $Fe(acac)_3$-catalyzed method to convert propargylic epoxide **93** into the corresponding trisubstituted allene **94** in 62% yield and good diastereoselectivity en route toward amphidinolide Y (Scheme 10, d).[31]



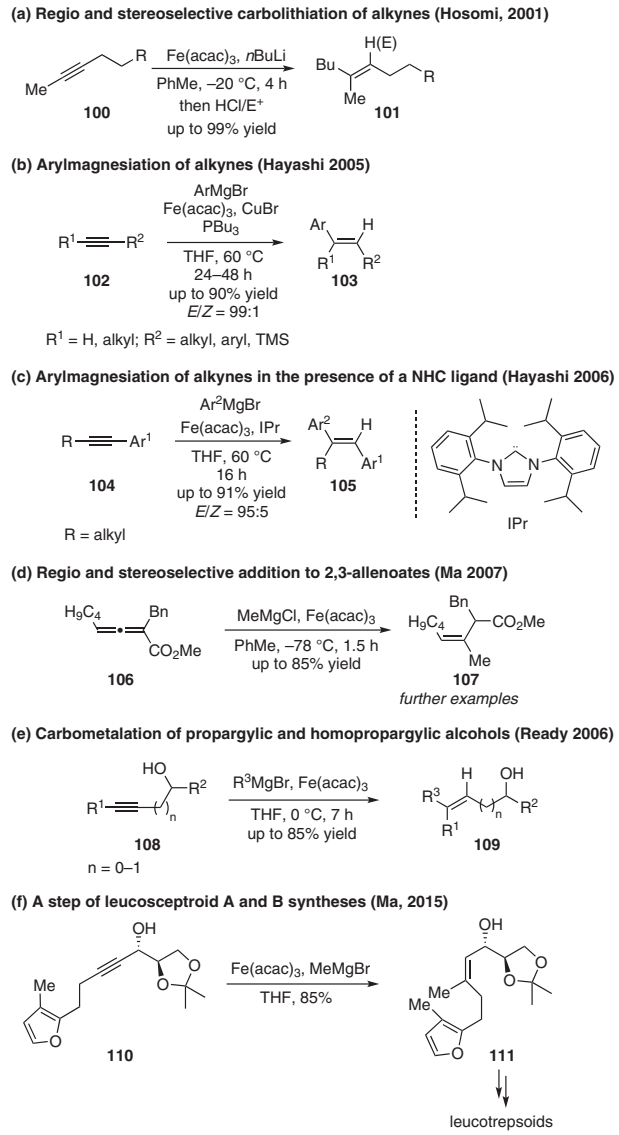
Scheme 10 (a) Synthesis of substituted allenes by Bäckvall,[28] (b) and (c) by Fürstner,[29,30] and (d) an excerpt from the total synthesis of amiphidinolide Y[31]

A broader field in the use of $Fe(acac)_3$ in alkyne chemistry is the benzannulation of aryl compounds. In 2011, Nakamura reported a [4+2] benzannulation between biaryl or 2-alkenylphenyl Grignard reagents **96** and alkynes **95** for the synthesis of polyaromatic compounds **97** (Scheme 11, a).[32] The scope is limited to aryl Grignard reagents but a variety of variations on alkynes **95** are possible. Optimized reaction conditions use catalytic amounts of $Fe(acac)_3$ and dtbpy as the ligand in the presence of 1,2-dichloro-*iso*-butane as oxidant, which was required to prevent partial polymerization of the alkyne. The use of aminoquinoline carboxamides **98** established the possibility to perform directed iron-catalyzed C–H bond activation, which was reported by Nakamura for the preparation of disubstituted indenones **99** in moderate to very good yields (Scheme 11, b).[33]



Scheme 11 (a) Nakamura's [4+2] benzannulation[32] between aryl Grignards and alkynes, and (b) synthesis of indenones;[33] dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl, DCIB = 1,2-dichloro-*iso*-butane, dppen = 1,2-bis(diphenylphosphino)ethylene

Carbometalations[34] of alkynes represent a highly stereo and regioselective tool for the synthesis of higher functionalized and tetrasubstituted olefins. Examples using catalytic amounts of $Fe(acac)_3$ for *syn*-carbometalations are discussed below (Scheme 12). In 2001, Hosomi and co-workers published a carbolithiation of internal alkynes **100** for the synthesis of higher substituted olefins **101** by using *n*-butyllithium and $Fe(acac)_3$ (Scheme 12, a).[35] The vinyl lithium intermediate could be trapped by electrophiles of any kind (H^+, D^+, $XSiR_3$, aldehydes, ketones), which makes this method applicable for a variety of different structures. Further variations of carbomagnesiations of alkynes were reported by Hayashi using catalytic amounts of $Fe(acac)_3$, either with CuBr[36] or a N-heterocyclic carbene ligand.[37] Using these conditions, Hayashi was able to obtain trisubstituted olefins **103** and **105** in very good yields and *E*:*Z* ratios (Scheme 12, b and c). In 2007, Ma and co-workers reported the regio and stereoselective addition of Grignard reagents to 2,3-allenoates **106** for the synthesis of β,γ-unsaturated trisubstituted olefins **107** (Scheme 12, d).[38] Carbometalations of propargylic and homopropargylic alcohols **108** with Grignard reagents have been reported by Ready with broad substrate scope and the possibility of trapping vinylmagnesium compounds with different electrophiles (e.g., H^+, D^+, $ZnCl_2$/NBS, aldehydes, CuCN/2LiCl/allyl bromide) (Scheme 12, e).[39] This carbomagnesiation procedure was applied by the Ma group for an alkyne methylation to obtain intermediate **111** for the total synthesis of leucosceptroids A and B (Scheme 12, f).[40]

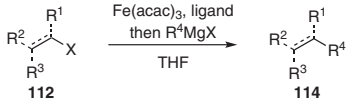


Scheme 12 (a) Hosomi's regio- and stereoselective carbolithiation of alkynes,[35] (b) and (c) arylmagnesiation of alkynes by Hayashi,[36,37] (d) regio and stereoselective addition of 2,3-allenoates with Grignard reagents by Ma,[38] (e) Ready's carbometalation of propargylic and homopropargylic alcohols,[39] and (f) application in Ma's total synthesis of leucosceptroids A and B[40]

5 Cross-Couplings and Cycloisomerizations

Cross-coupling reactions have become irreplaceable tools for the synthesis of C–C bonds at sp, sp^2 and sp^3 hybridized carbon atoms bearing a wide range of residues on both sides of the reaction partners. One of the first described approaches using palladium or nickel as metals for this kind of transformation was the coupling of Grignard reagents with aryl or vinyl halides by Kumada and co-workers.[41] As far back as 1941, the first Fe-catalyzed cross-cou-

pling was reported by Fields and Kharash, the value of which only became apparent a few decades later.[42] The substrate scope of Fe-catalyzed cross-coupling reactions is extremely broad since aliphatic substrates are also compatible with this method. Therefore, it is an even more powerful C–C bond-forming reaction compared to the corresponding Pd-catalyzed transformations (Scheme 13).

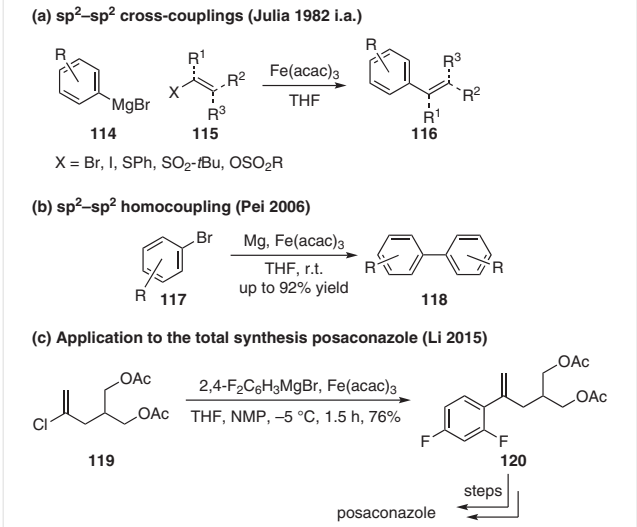


Scheme 13 General procedure for Fe(acac)$_3$-catalyzed cross-couplings

Oxidations states ranging from Fe(–II) up to Fe(III) species are proposed to be involved in the catalytic cycle depending on the type of cross-coupling. In most cases the initial step is the in situ reduction of Fe(acac)$_3$ to a low valent iron species. The different mechanisms are reviewed elsewhere.[43,44] Even though reactive intermediates are difficult to characterize experimentally, the formation of the intermediary ate-complexes was at least confirmed by the group of Koszinowski who found evidence for Fe(III), Fe(II) and Fe(I) species via electrospray ionization mass spectrometry. Further investigations suggested that product formation occurred from a [Ph$_3$Fe^{III}*i*Pr]$^-$ complex (in the case of a PhMgBr to *i*PrCl coupling) to give [Ph$_2$Fe(I)]$^-$ and Ph*i*Pr as the desired product.[45]

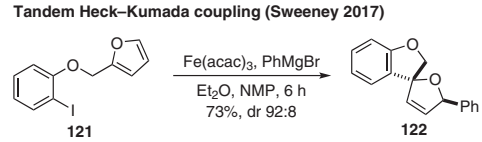
5.1 Fe-Catalyzed sp^2–sp^2 Cross-Coupling Reactions

Transition-metal-catalyzed sp^2–sp^2 cross-coupling reactions were first reported by Julia and co-workers. They investigated the reaction between *tert*-butyl sulfones with phenylmagnesium bromide using different metal acetoacetonates (Scheme 14, a).[46a] In contrast, Knochel and co-workers used either aromatic Grignard reagents or the corresponding cuprates in cross-coupling reactions with vinyl halides or sulfonyl enols. These conditions were even compatible with intramolecular ester moieties on the organometallic reagent (Scheme 14, a).[46b,c] On the other hand, the use of phenyl thioethers only allows minor substitution pattern variability on the aromatic system (Scheme 14, a).[46d] The first homo-coupling of two halogenated aromatic compounds via in situ formation of the Grignard reagent gave access to dimeric compounds **118** and was also applicable to aliphatic halides (Scheme 14, b).[47] Since there is a large variety of Fe(acac)$_3$-catalyzed cross-couplings in synthetic chemistry, only selected examples will be mentioned briefly. The group of Li used a sp^2–sp^2 cross-coupling between 2,4-F$_2$C$_6$H$_4$MgBr and vinyl chloride **119** to construct the carbon skeleton of the eastern fragment **120** of posaconazole in 76% yield (Scheme 14, c).[48]



Scheme 14 (a) Fe-catalyzed sp^2–sp^2 cross-couplings of aryl and vinylic substrates,[46] (b) sp^2–sp^2 homo-coupling,[47] and (c) Fe-catalyzed cross-coupling towards the total synthesis of posaconazole;[48] NMP = *N*-methylpyrrolidine

Sweeney and co-workers were able to establish a tandem Heck–Kumada cross-coupling reaction to construct dihydrofuran **122** in high yield and diastereoselectivity.[49] The stereochemical outcome can be rationalized by the disfavored steric interactions of the iron residue and the C–H bond at the *ortho* position of the aromatic ring (Scheme 15).



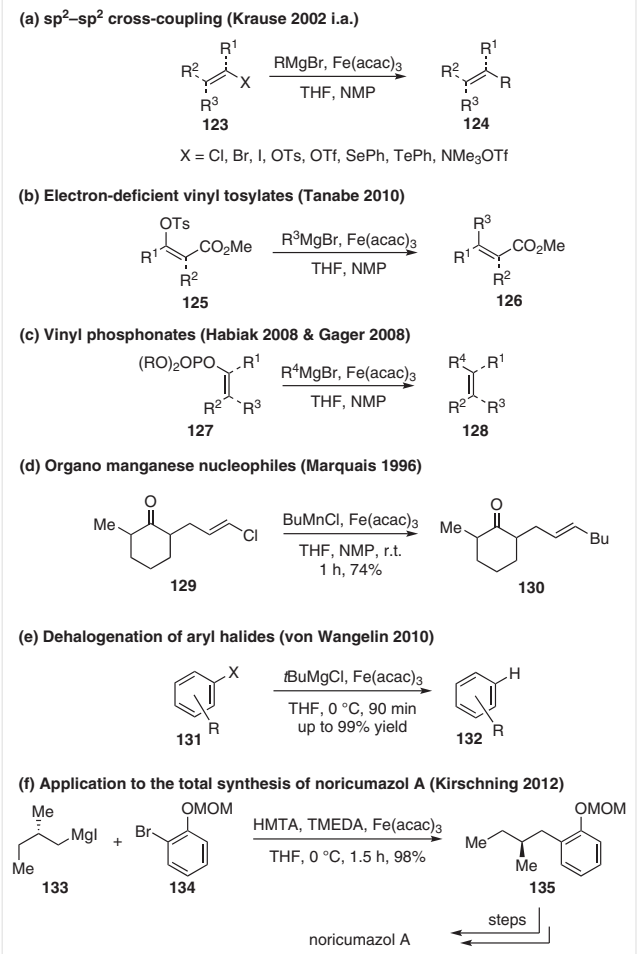
Scheme 15 A tandem Heck–Kumada cross-coupling reported by Sweeney and co-workers[49]

5.2 Fe-Catalyzed sp^2–sp^3 Cross-Coupling Reactions

Fe-catalyzed sp^2–sp^3 (electrophile–nucleophile) cross-couplings offer the advantage of not undergoing β-hydride eliminations in contrast to palladium-catalyzed cross-couplings. The use of aliphatic Grignard reagents requires NMP as a co-solvent. It is proposed to be essential for the formation of the [Mg(NMP)$_6$][FeMe$_3$]$_2$ complex, which is pivotal for high selectivities using aliphatic Grignard reagents.[50]

The cross-coupling of vinyl or aryl electrophiles with aliphatic Grignards tolerates a wide variety of functional groups such as different electron-withdrawing or electron-donating groups on the electrophile. Furthermore, ester moieties are also compatible with these organometallic species. Thus, electrophiles such as Cl, Br, I, OTs, OTf, SePh, TePh and NMe$_3$OTf can be employed in Fe(acac)$_3$-mediated cross-couplings, delivering the desired products in good to

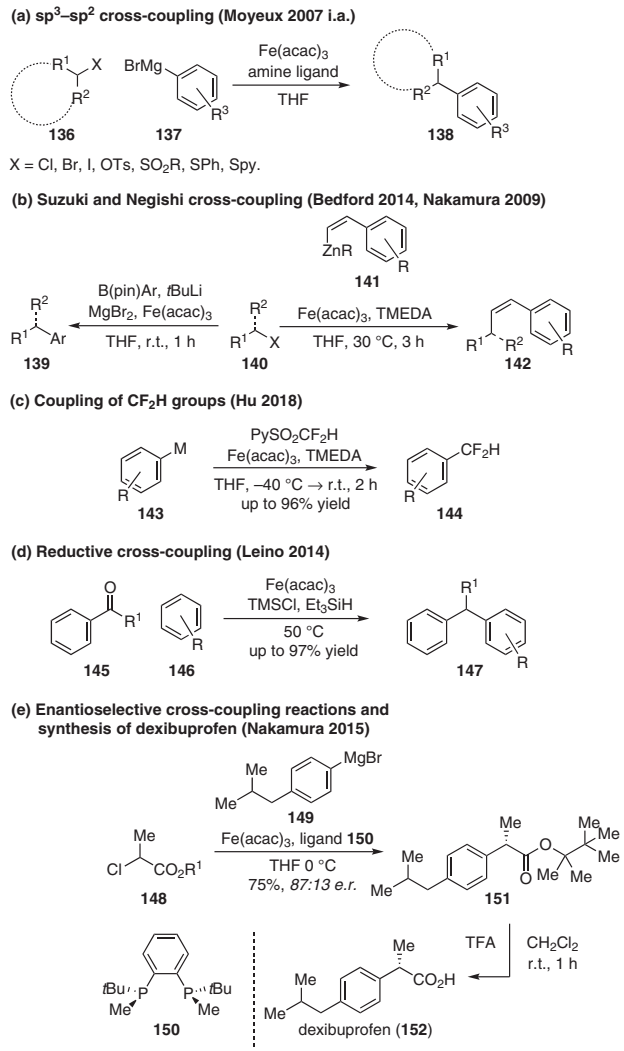
high yields and good diastereoselectivities (Scheme 16, a).[43c,51] Furthermore, even more complex substrates exhibiting polyaromatic, bridgehead, allyl amine or vinyl alkynyl motifs are also compatible with this methodology. In particular, tosyl-substituted Michael acceptors such as **125** can be joined to aliphatic residues to give access to highly substituted double bonds with excellent control of the double bond geometries (Scheme 16, b).[52] Moreover, the use of enol phosphonates **127** was reported by the Habiak and Gagner groups. These substrates can easily be synthesized from the corresponding ketones and are easier to handle on large scale compared to their corresponding triflates.[53] In continuation of their contribution on these enol phosphonates, the substrate scope could be enlarged to conjugated phosphonate dienes (Scheme 16, c).[53] As $Fe(acac)_3$-catalyzed cross-couplings tolerate a large variety of functional groups, Marquais and co-workers used manganese instead of Grignard nucleophiles to broaden the substrate scope to ketones (Scheme 16, d).[54a] In addition, the tolerance of Grignard reagents to ketones was reported by Cahiez in 2009.[54b] Besides coupling to carbon residues, $Fe(acac)_3$ and *t*BuMgCl can be used for dehalogenation. The proposed mechanism involves hydride transfer from the *t*Bu group to the Fe-arene species, which then undergoes reductive elimination (Scheme 16, e).[55] The application of $Fe(acac)_3$-mediated sp^2–sp^3 cross-couplings in total synthesis was, amongst others,[1,56] demonstrated by the Kirschning group in their total synthesis of noricumazol A. The $Fe(acac)_3$-catalyzed C–C bond formation between MOM-protected phenol **134** and alkyl Grignard species **133** gave the core of the eastern fragment **135** in an excellent yield (Scheme 16, f).[57]



Scheme 16 (a) Fe-catalyzed sp^2–sp^3 cross-couplings with different substrates,[51] (b) cross-couplings on Michael acceptors,[52] (c) vinyl phosphonate–sp^2 cross-coupling,[53] (d) an organo manganese nucleophile which tolerates ketones,[54] (e) dehalogenation of aryl halides,[55] and (f) a $Fe(acac)_3$-catalyzed cross-coupling for the synthesis of the eastern fragment core of noricumazol A;[57] HMTA = hexamethylenetetraamine, TMEDA = tetramethylethylenediamine

5.3 Fe-Catalyzed sp^3–sp^2 Cross-Coupling Reactions

Fe-catalyzed sp^3–sp^2 cross-couplings of aromatic Grignard reagents to primary or secondary electrophiles make use of a large variety of substrates. Cyclic or linear aliphatic starting materials as well as halogenated azetidines deliver good to excellent yields in cross-coupling reactions.[58] The use of thioethers as electrophiles in cross-coupling reactions has been described by Denmark and co-workers using phenyl and pyridinyl thioethers or sulfones (Scheme 17, a).[58d] Furthermore, modified Suzuki[59] cross-coupling reactions have been reported by the Bedford group.[60] They used *t*BuLi to activate the boron species as its ate-complex, followed by Lewis acid activated C–C bond formation (Scheme 17, b). Nakamura and co-workers developed a protocol for the sp^3–sp^2 Negishi[61a] coupling with substrates bearing esters or nitriles on the aliphatic side chain (Scheme 17, b).[61b] Hu's group developed conditions for coupling CF_2H groups to organozinc or magnesium compounds, while Zhang and co-workers reported a Pd-Fe co-catalyzed coupling of CF_2H groups involving a CF_2 carbene intermediate (Scheme 17, c).[62,63] Beginning with benzaldehyde, Leino designed an in situ reduction of a carbonyl group to its corresponding chloride followed by coupling to the second aryl unit (Scheme 17, d).[64] The introduction of chirality toward the sp^3-hybridized C-atom was first accomplished in an $Fe(acac)_3$-mediated cross-coupling by Nakamura in 2015.[43e] Originating from racemic α-chloro ester **148** the enantioenriched coupling product **151** was obtained in an enantiomeric ratio (e.r.) of 87:13 and 75% yield. This transformation was most effective with R^2 being a methyl group (Scheme 17, e). Further cleavage of the theptyl ester delivers free acid dexibuprofen (**152**), which can be co-crystallized with octylamine to enhance the e.r. up to >99:1.[43e]

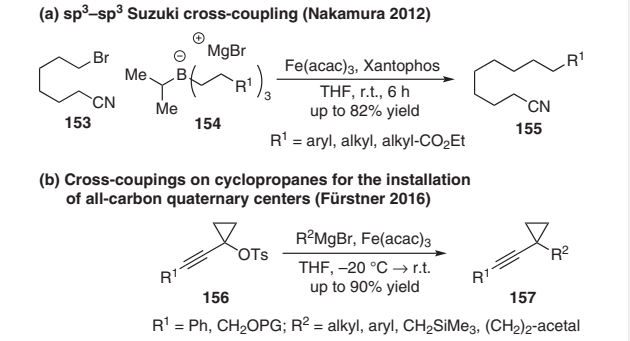


Scheme 17 (a) Fe-catalyzed sp^3–sp^2 cross-couplings to aryl Grignard reagents,[58] (b) Suzuki and Negishi modifications,[60,61b] (c) cross-coupling to CF_2H groups,[62,63] (d) in situ reductive cross-coupling,[64] (e) enantioselective cross-couplings and application to the synthesis of dexibuprofen[43e]

5.4 Fe-Catalyzed sp^3–sp^3 Cross-Coupling Reactions

Fe-catalyzed sp^3–sp^3 cross-couplings are not as widespread as sp^2–sp^3 cross-coupling reactions. On the other hand, they possess high potential for the installation of C–C bonds at sp^3-hybridized positions of complex molecules.

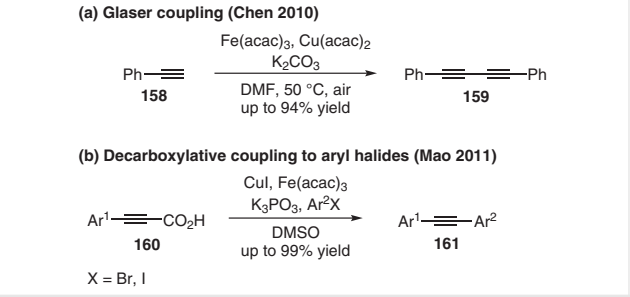
Nakamura and co-workers used in situ hydroboration of terminal olefins followed by formation of the isopropylmagnesium bromide ate complex **154** to couple these activated boron nucleophiles to aliphatic halides.[43d] It should be mentioned that this transformation is also compatible with functional groups such as nitriles or esters (Scheme 18, a). Fürstner and co-workers applied $Fe(acac)_3$ cross-couplings to tosylated alkynyl cyclopropanes **156**.[65] Their protocol provided all-carbon quaternary centers in good to excellent yields, whilst tolerating synthetically useful functional groups (Scheme 18, b).



Scheme 18 (a) Fe-catalyzed sp^3–sp^3 Suzuki cross-couplings by Nakamura,[43d] and (b) Fürstner's cross-couplings on cyclopropanes[65]

5.5 Fe-Catalyzed Cross-Coupling Reactions at sp Centers

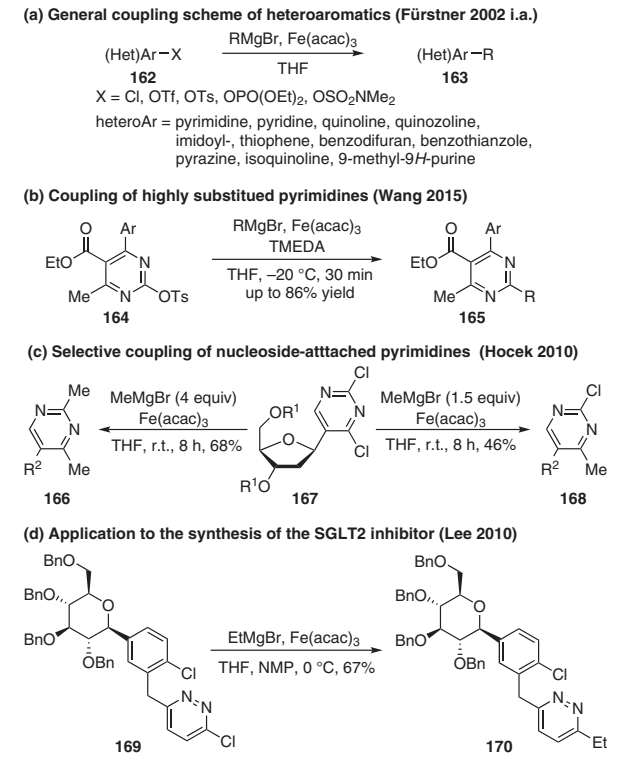
Similar to sp^3–sp^3 cross-couplings, transformations at sp-hybridized carbons are a remaining challenge. In this context, Meng and co-workers developed conditions for the homo-Glaser reaction of alkyne **158** with $Fe(acac)_3$ and $Cu(acac)_2$ as the co-catalyst (Scheme 19, a).[66] Furthermore, not only are sp–sp couplings possible, but also combinations with sp^2-hybridized halides. The nucleophilic alkyne **160** was activated by decarboxylation or direct C–H oxidation at 140 °C (Scheme 19, b).[67]



Scheme 19 (a) Alkyne couplings in Glaser fashion,[66] and (b) decarboxylative coupling of alkynes with aryl halides[67]

In the context of $Fe(acac)_3$-catalyzed heteroarene syntheses there are only a limited number of methodology reports. However, there are numerous applications in total syntheses. Many of these have been summarized by Szostak and co-workers.[56] A selected variety of $Fe(acac)_3$-catalyzed cross-coupling reactions are illustrated in Scheme 20 (a). In most cases, chlorides are used to provide good selectivities for the cross-coupling reactions as the carbon–chlorine bond is the preferred site for Fe insertion.[43b,c,51e,68] Furthermore, nitrogen-directed cross-coupling of heteroarenes can be performed regiospecifically under mild conditions. The

substrate scope for generating tetrasubstituted pyrimidines **164** could be further extended by using tosylates or halides as coupling partners (Schemes 20, b and c).[69,70] One example of how far this methodology can be extended was described by the group of Lee in their synthesis of SGLT2 inhibitor **170**.[71] They employed a sp^2–sp^3 cross-coupling reaction during the late stage of their synthesis and did so by differentiating between two distinct aryl chlorides (Scheme 20, d).



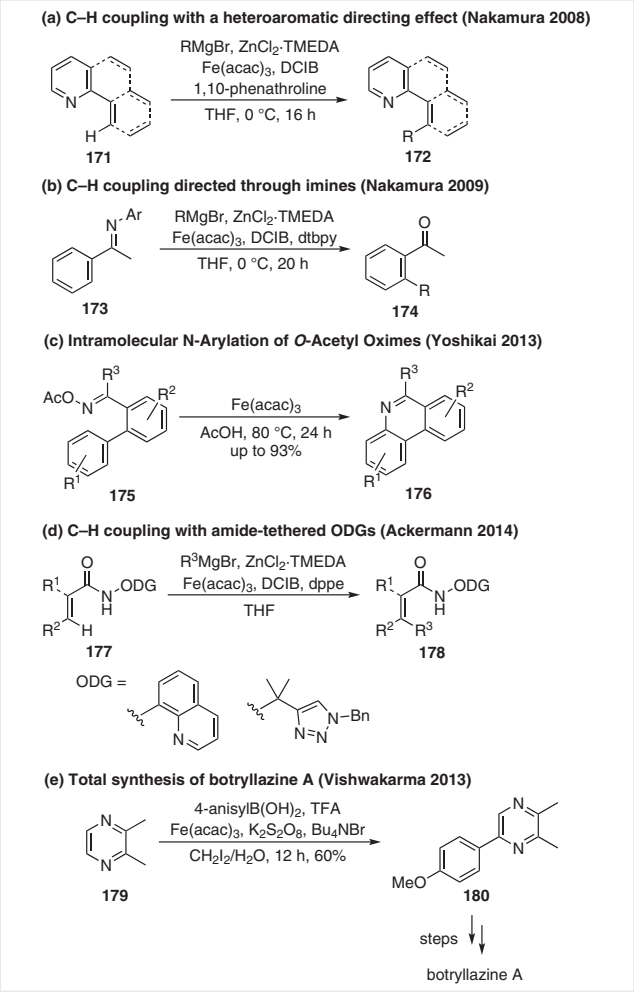
Scheme 20 (a) General approach to cross-couplings of heteroarenes,[43b,c,51e,68] (b) selected examples of sterically challenging substrates,[69] (c) couplings on nucleosides,[70] and (d) application to the total synthesis of the SGLT2 inhibitor **170** by Lee and co-workers[71]

5.6 Fe-Mediated Functionalization of C–H Bonds

Common cross-coupling reactions require functional groups at specific positions to generate the new C–C bond regiospecifically. In contrast, the direct functionalization of C–H bonds partially simplifies this classical approach. To compensate for the omitted functional group, an external directing group is required to achieve good regio- and diastereoselectivity.[1] Nakamura and co-workers reported such cross-coupling reactions under iron(III) catalysis on benzoquinoline system **171**, directing the metal selectively to the γ-position of the aromatic nitrogen (Scheme 21, a).[72] Further extensions of this work led to non-cyclic imines that were used for direct *ortho*-functionalization of arenes (Scheme 21, b).[73] Interestingly, if an acetylated oxime is in proximity to the *ortho*-position N-arylation takes place (Scheme 21, c).[74] Besides aromatic substrates, the methodology was expanded to unsaturated amides. An additional *ortho* directing group (ODG) attached to the nitrogen is essential for coordinating the iron catalyst. This in turn is pivotal for the regioselective C–H activation and for controlling the double bond geometry (Scheme 21, d).[75] Vishwakarma and co-workers reported $Fe(acac)_3$-catalyzed Suzuki cross-coupling reactions of aryl boronic acids to pyrazine C–H bonds instead of C–halide bonds. This method was used for the installation of the aryl–pyrazine bond in the synthesis of botryllazine A (Scheme 21, e).[76]

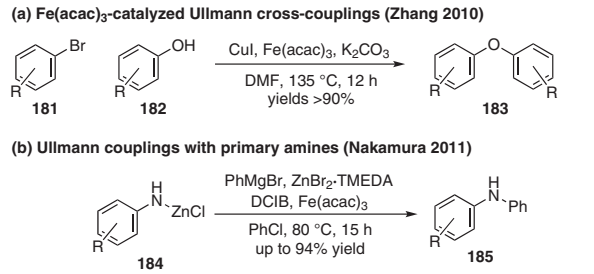
5.7 Fe-Catalyzed Ullmann Coupling Reactions

Applications in the Ullmann coupling for the construction of biaryl ethers in excellent yields were published by



Scheme 21 (a) Coupling of Grignard reagents to arene C–H bonds,[72] (b) and (c) C–H coupling directed through imines,[73,74] (d) C–H coupling through amide-tethered ODGs,[75] and (e) intermolecular CH coupling in Suzuki fashion;[76] DCIB = 1,2-dichloro-*iso*-butane, dtbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridine, dppe = 1,2-bis(diphenylphosphino)ethane)

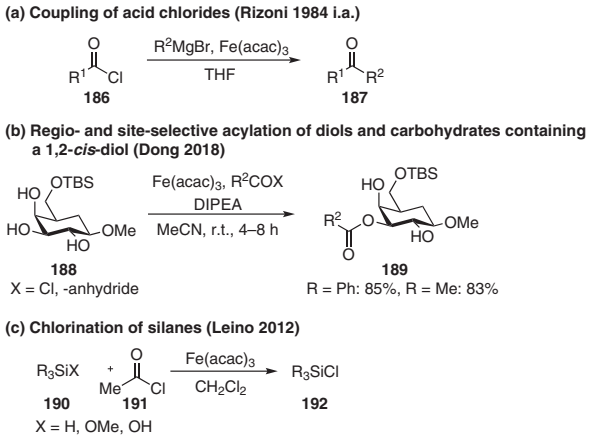
the Zhang group, who used a copper–iron co-catalyst system (Scheme 22, a).[77a–c] Further investigations led to double Ullmann reactions with 1,4-diiodo arenes, which can also be expanded to macrocyclizations of polyarylethers.[77d] Parallel to their work on biaryl ethers, Nakamura and co-workers investigated the coupling of primary aryl amines which were converted into the zincate and subsequently used for secondary amine formation (Scheme 22, b).[78]



Scheme 22 (a) $Fe(acac)_3$-catalyzed Ullmann–Goldberg cross-couplings,[77c] and (b) Ullmann coupling of amines;[78] DCIB = 1,2-dichloro-*iso*-butane

5.8 Fe-Catalyzed Cross-Coupling of Acyl Chlorides

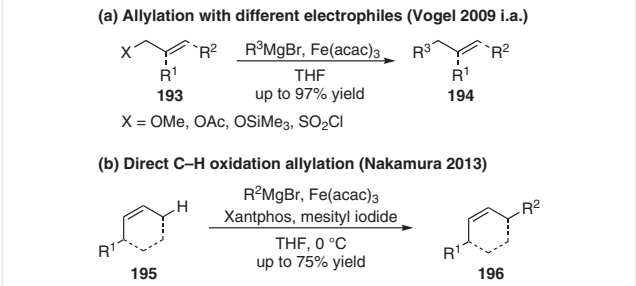
Earlier, in 1984, Ronzini and co-workers described the $Fe(acac)_3$-catalyzed cross-coupling of acyl chlorides to aliphatic or aromatic Grignard reagents (Scheme 23, a),[79a] and this research was later continued by the Fürstner group.[79b] The Dong group used $Fe(acac)_3$ for the regio- and site-selective acylation and benzoylation of diols and carbohydrates (Scheme 23, b).[80] The reagents of choice were the corresponding acyl chloride, Hünig's base and catalytic amounts of $Fe(acac)_3$, which afforded the corresponding selectively protected alcohols 189. While the common use of acyl chlorides is in coupling of the carbonyl moiety to other nucleophiles, the Leino group published a method for the chlorination of silanes 190 (Scheme 23, c).[81]



Scheme 23 (a) Coupling of activated acyl chlorides to different Grignard reagents,[79] (b) selective protection of carbohydrates,[80] and (c) reversed reactivity of acyl chlorides for the synthesis of silyl chlorides[81]

5.9 Fe-Catalyzed Allylations

The Fe-catalyzed allylation of either aromatic or aliphatic Grignard reagents is possible by using allyl ethers or sulfonyl chlorides as electrophiles (Scheme 24, a).[82] Furthermore, the direct functionalization of allylic C–H bonds was reported by Nakamura and co-workers, which was also applicable to different substitution patterns on the allylic reagent (Scheme 24, b).[83]

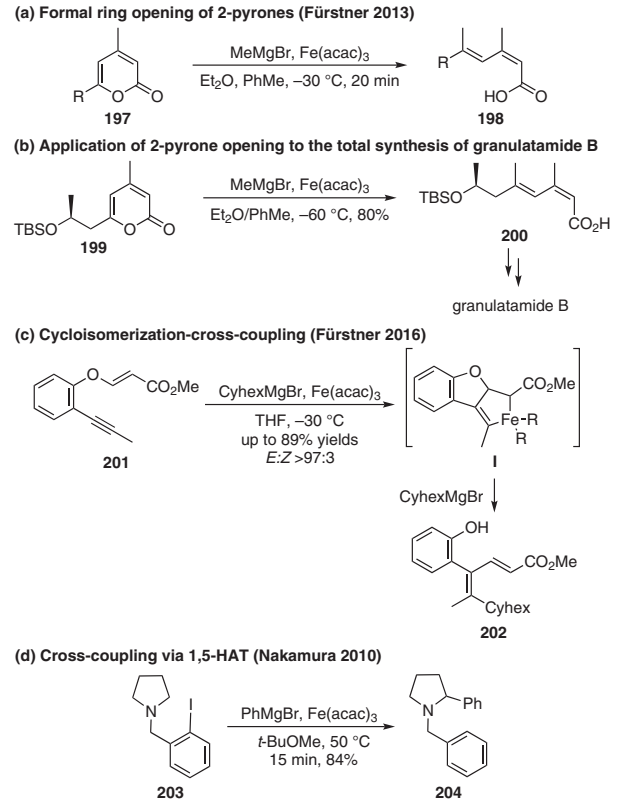


Scheme 24 (**a**) Electrophile allylations,[82] and (**b**) direct C–H allylation[83]

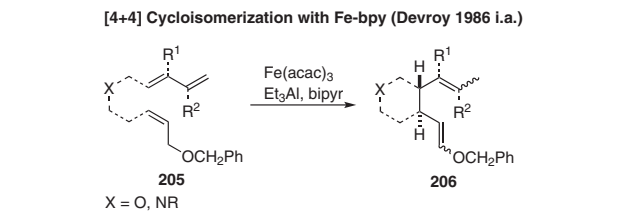
5.10 Miscellaneous Fe-Catalyzed Cross-Coupling Reactions

Further applications using $Fe(acac)_3$ were reported by Fürstner as a highly diastereoselective method for simultaneous ring-opening of 2-pyrones **197** (Scheme 25, a).[84] This transformation is mechanistically proposed as 1,6-addition and reversion with the carboxylate as the leaving group. Furthermore, this strategy was used for the installation of the *Z*/*E* diene moiety of granulatamide B in >10:1 d.r. (Scheme 25, b).[84] Fürstner and Echeverria developed further reaction types of low-valent iron generated from Fe(III), where the iron reacts in a metalla-Alder-ene fashion with the ene–yne system to form metallacycle **I** (Scheme 25, c).[85] Instead of a direct reductive elimination, the addition of Grignard reagents opens the five-membered ring followed by reductive elimination of Fe(I) to build up the tetrasubstituted double bond of **202**. The Nakamura group developed a protocol for insertion of iron into phenyl-iodo bonds followed by a 1,5-HAT (Scheme 25, d).[86] The so-generated organoiron intermediate behaves similarly to established sp^2–sp^3 couplings. Overall, this transformation allows access to α-functionalized pyrrolidines.

Devroy and co-workers used Fe-bpy, which was prepared from $Fe(acac)_3$ in situ and investigated the [4+4] cycloisomerization of dienes with allyl ethers (Scheme 26).[87] This transformation was also applied intramolecularly for amine- or ether-tethered substrates to give the corresponding *trans*-fused six-membered rings **206**.[87]



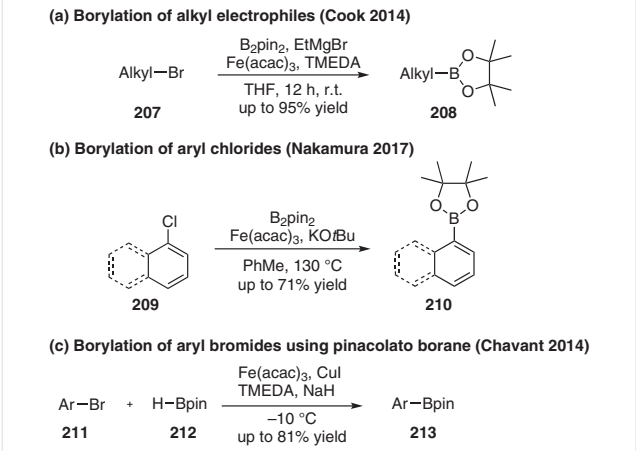
Scheme 25 (a) Opening of 2-pyrones to highly substituted dienes,[84] (b) application of this method toward the total synthesis of granulatamide B,[84] (c) Fürstner's cycloisomerization–cross-coupling approach,[85] and (d) a tandem 1,5-HAT–Kumada cross-coupling[86]



Scheme 26 Fe-byp-catalyzed [4+4] cycloisomerization of dienes with allylic ethers[87]

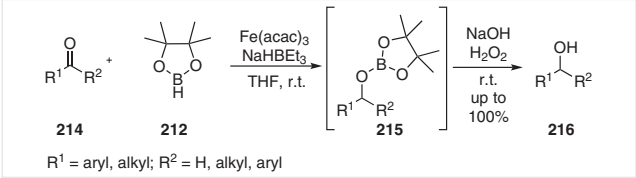
6 Borylations

Besides the tremendously broad field of $Fe(acac)_3$-mediated cross-couplings, borylations of alkyl or aryl halides have been reported in the literature. In 2014, Cook and coworkers published the borylation of various alkyl halides **207** with bispinacolato diboron and provided a very broad scope of substrates **208** (Scheme 27, a).[88] The electrophiles of choice were chlorides, bromides, iodides and tosylates, with bromides giving the best results in up to 95% yield. Borylations of aryl chlorides **209** were reported by Nakamura in 2017 using bispinacolato diboron in the presence of potassium *tert*-butoxide at elevated temperature, albeit with a limited substrate scope (Scheme 27, b).[89] Coupling of pinacolato borane **212** with aryl bromides **211** using iron–copper catalysis has been described by Chavant in yields of up to 81% (Scheme 27, c).[90]



Scheme 27 (a) Cook's borylation of sp^3 electrophiles,[88] (b) Nakamura's borylation of aryl chlorides,[89] and (c) Chavant's borylation of aryl bromides[90]

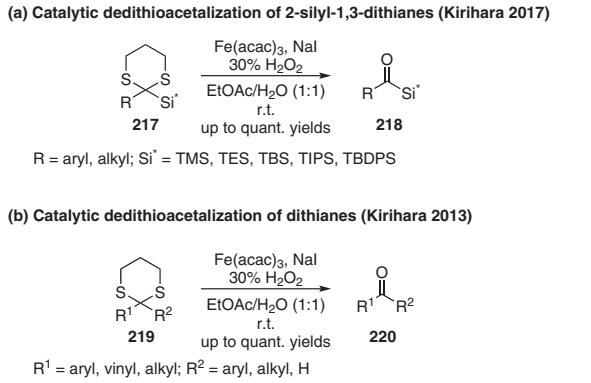
In 2017 Findlater and Tamang showed that it was possible to obtain the corresponding alcohol **216** through the Fe-catalyzed hydroboration of aldehydes or ketones **214**. It is proposed that this reaction proceeds via alkoxyboron species **215**, which delivers alcohol **216** under standard work-up conditions (Scheme 28).[91]



Scheme 28 Hydroboration of aldehydes and ketones by Findlater and Tamang[91]

7 Miscellaneous Reactions

Additional transformations highlight the great potential of $Fe(acac)_3$ catalysis and synthesis. The Kirihara group published a selective and efficient method for dedithioacetalizations of 2-silylated 1,3-dithianes **217**. In these transformations the use of $Fe(acac)_3$ in combination with NaI and hydrogen peroxide greatly improves the yields of the corresponding acyl silanes **218** compared to other well-established protocols (Scheme 29, a).[92] The same conditions were applied for oxidative cleavage of aryl-, vinyl-, and alkyl-substituted dithianes **219** in up to quantitative yields (Scheme 29, b).[93]

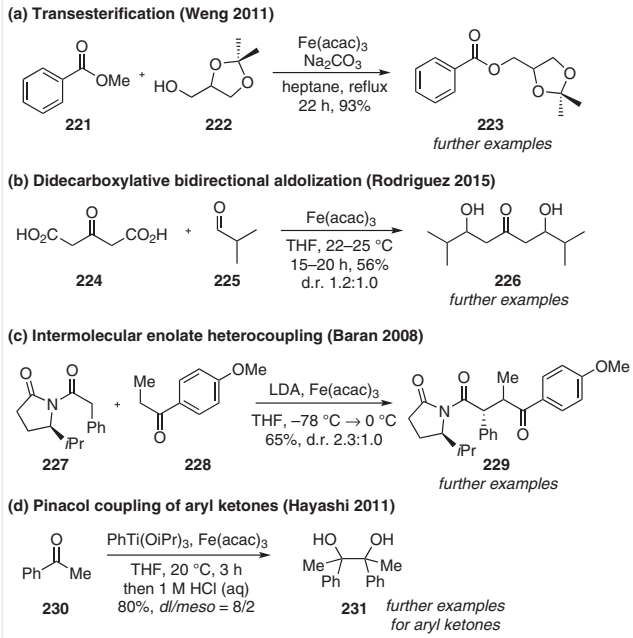


Scheme 29 (a) Catalytic dedithioacetalization of dithianes to obtain acyl silanes,[92] and (b) aldehydes or ketones[93]

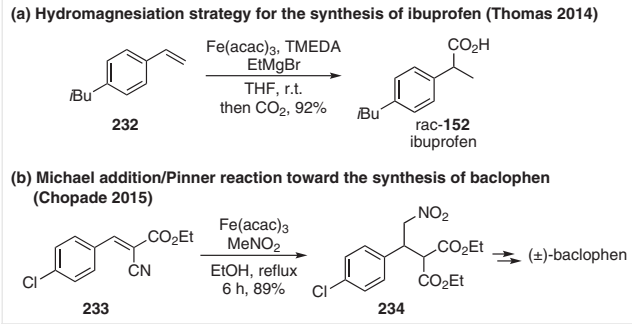
A tremendously broad scope of substrates for transesterifications of different alcohols with different esters was described by Weng and co-workers in 2011 (Scheme 30, a).[94] An approach toward the diversity-oriented ketodiol **226** via didecarboxylative bidirectional aldolization of diacid **224** was published by Rodriguez (Scheme 30, b).[95] A different type of reaction is the intermolecular heterocoupling of enolates described by the Baran group to synthesize the corresponding 1,4-diketones **229** (Scheme 30, c). The mechanism is proposed to proceed via an oxidative radical phenol coupling type mechanism.[96] Further, Hayashi and Saski published a pinacol coupling of aryl ketone **230** with a phenyltitanium reagent in the presence of $Fe(acac)_3$ to afford the corresponding pinacol **231** (Scheme 30, d).[97] The initial step is a reductive cross-coupling of the phenyl substituent to generate a low-valent titanium species. This titanium species subsequently catalyzes the pinacol coupling.

An additional variation to carbometalations of alkynes and allenes is the hydromagnesiation of olefins. Subsequent addition of carbon dioxide generates the corresponding carboxylic acids. This was applied by Thomas and co-workers to the synthesis of ibuprofen rac-(**152**) (Scheme 31, a).[98] (±)-Baclophen[99a] and (±)-rolipram[99b] were synthesized due to their pharmacological relevance via an $Fe(acac)_3$-mediated Michael addition of nitromethane to α-cyano cinnamic ester **234** (Scheme 31, b).[99]

A rather mild approach for the reduction of nitroarene **235** with different substitution patterns to the corresponding anilines **236** was published by Lemaire and co-workers in 2010 (Scheme 32).[100] This iron-mediated reduction in the presence of TMDS tolerates various functional groups, such as esters, aldehydes, carboxylic acids, bromides, etc., and affords the corresponding anilines **236** as the hydrochloride salts in excellent yields (Scheme 32, a). In 2018, Gennari and co-workers[101] published an asymmetric reduction of imine **237** using a modified chiral Knölker-type catalyst[102] and obtained, in the presence of $Fe(acac)_3$, high conversions with moderate selectivities (Scheme 32, b). Another



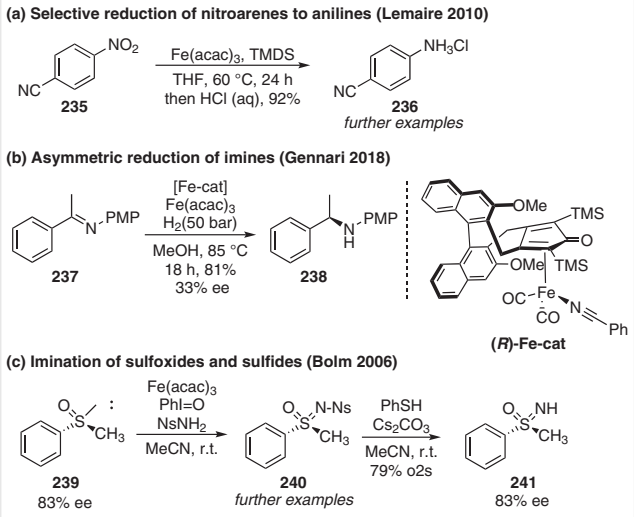
Scheme 30 (a) Selected example of Weng's transesterification,[94] (b) didecarboxylative bidirectional aldolization by Rodriguez,[95] (c) Baran's intermolecular enolate heterocoupling,[96] and (d) Hayashi's pinacol coupling of aryl ketones[97]



Scheme 31 Synthesis of small, medicinally relevant molecules: (a) Hydromagnesiation toward the synthesis of ibuprofen by Thomas,[98] and (b) synthesis toward baclophen by Chopade[99]

$Fe(acac)_3$-mediated reaction is Bolm's imination of sulfoxide **239** which proceeds with complete retention of configuration at the sulfur center and affords sulfoximine **241**.[103] The same transformation is applicable to sulfides and provides sulfimines in very good yields (Scheme 32, c).[103]

The synthesis of several heterocyclic structures has been shown in the field of $Fe(acac)_3$-mediated synthetic chemistry.[56] In 2010, Yoon and Williamson published a synthetic access to 1,3-oxazolidines **243** by aminohydroxylation of olefins **242** using *N*-sulfonyl oxaziridines (Scheme 33, a).[104] This aminohydroxylation strategy was applied to the synthesis of (±)-octopamine.[104] Bao employed radical conditions for the synthesis of 3-amido-oxindole **246** from

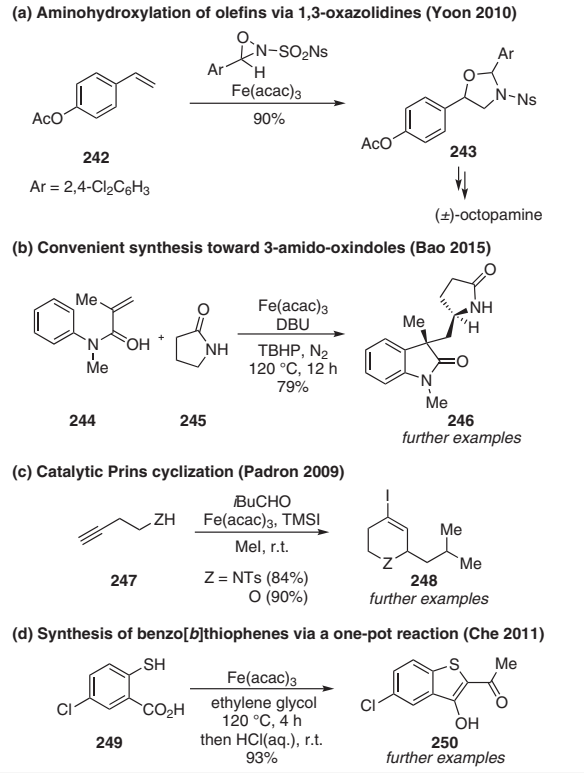


Scheme 32 (a) Selective reduction of nitroarenes to anilines by Lemaire,[100] (b) asymmetric reduction using chiral (cyclopentadienone)iron complexes by Gennari,[101] and (c) imination of sulfoxides and sulfides by Bolm;[103] TMDS = 1,1,3,3-tetramethyldisilazane, Ns = nosyl, o2s = yield over two steps.

aromatic *i*-propenylamides **244** and γ-butyrolactam **242** (Scheme 33, b).[105] Furthermore, Prins cyclizations of homopropargylic alcohols and amines **247** were reported by Padrón and co-workers (Scheme 33, c).[106] By using aldehydes in combination with TMSI the iodinated unsaturated heterocycle **248** was obtained. A very different example is the synthesis of benzo[*b*]thiophenes **250** by Che in 2011.[107] They demonstrated that Fe(acac)$_3$ is not only the catalyst but also the source of acetylacetone as the reagent. Therefore, one ligand on the iron is exchanged by thiosalicylic acid **249** and thus liberates acetylacetone for the subsequent transformation (Scheme 33).[107]

8 Conclusions

Even though Fe(acac)$_3$ is broadly applicable in organic synthesis, a large variety of improvements are observed in the area of cross-coupling reactions. The remarkable functional group tolerance as well as its applicability to alkyl reagents illustrates the significance of Fe(acac)-catalyzed cross-coupling reactions. Additionally, the field of HAT-initiated transformations enables new pathways to complex natural products. Considering the relatively young area of this research, one can anticipate even more relevant contributions in the future.



Scheme 33 (a) 1,3-Oxazolidine formation by Yoon,[104] (b) synthesis of 3-amido-oxindoles by Bao,[105] (c) catalytic Prins cyclization by Padrón,[106] and (d) synthesis of benzo[*b*]thiophenes by Che[107]

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