



## Review on Fe-Catalyzed Carbon-Carbon, Carbon-Heteroatom Oxidative Coupling Reactions: En route to Heterocycles

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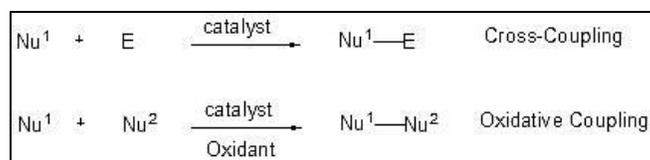
### ABSTRACT

Iron-catalyzed oxidative coupling between two C-H bonds, and C-H with heteroatom-H bonds have received significant attention due to its atom-economy, and sustainable nature. Oxidative coupling and annulations strategy provide step-economy route towards the synthesis of heterocycles. This review highlights the Fe-catalyzed C-C and C-heteroatom oxidative coupling reactions and its potential application in the synthesis of heterocycles, bioactive natural products.

**Keywords:** Oxidative coupling; C-C coupling; C-N coupling; Heterocycle

### INTRODUCTION

Over the past decades, transition-metal (TM) catalyzed coupling reactions have provided significant innovation for organic synthesis. Now-a-days, the coupling reactions constitute an efficient method for the construction of carbon-carbon and carbon-heteroatom bonds [1]. Along with rapid progress in organometallic chemistry, different combination of metal/ligand systems were developed and employed in the coupling reactions, thus greatly improving their applicability and efficiency [2-4]. Most reactions have focused on cross-coupling between electrophiles with nucleophiles [5]. However, judiciously tuning the reaction conditions and substrate molecules, coupling between two nucleophiles can be possible; the reaction is known as oxidative coupling (Scheme 1) [6-10]. In this process, additional oxidant is required to remove two extra electrons for the bond formation. Oxidative coupling between two C-H bonds and C-H bonds with heteroatom-H bonds is attractive because the reaction avoids the use of pre-functionalized starting materials, employs simple C-H, heteroatom-H containing substrates and provides step-economy, atom-economy synthesis of target molecules [11]. In addition, oxidative coupling and annulation strategy allow modular assembly of regioselectively decorated heterocycles which act as scaffold for numerous natural, non-natural products, drug molecules and functional materials [11,12]. In the last ten years, TM-catalyzed and mediated oxidative coupling between two C-H bonds, and C-H with heteroatom-H bonds towards C-C and C-heteroatom bond formation have received paramount attention. Most efforts were focused on the use of precious late transition metal catalysts, such as Pd, Rh, Ru, Ir, and Pt etc. [13-18]. However, cost and toxicity associated with these metals urge for the development of easily accessible, cheap and environmentally benign iron catalyst for the oxidative coupling reactions, which own obvious advantage and unique features.



Scheme 1: Comparison between cross-coupling and oxidative coupling

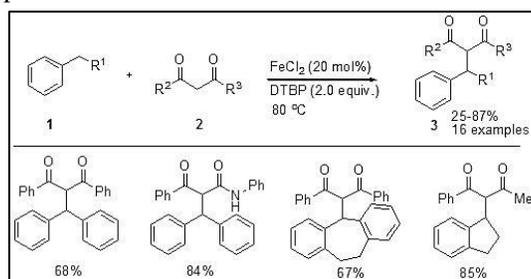
Iron is one of the most abundant metals on earth crust. It has a wide range of oxidation states,  $-II$  to  $+VIII$ , although all the oxidation state has never so far been reached. The most common oxidation states are  $+II$  and  $+III$ . When iron forms complex with  $\pi$ -acidic ligands, such as  $CO$ ,  $NO$ , bipy etc., it can reach  $0$ ,  $-I$  or  $-II$  oxidation states. The positive oxidation states of iron such as  $+IV$ ,  $+V$  and  $+VI$ , are all unstable and act as oxidants. Due to its ready accessibility both in elemental and compound form, Iron plays vital roles in fundamental biological processes [19]. The easy conversion of iron into its corresponding salts and complexes make it attractive for synthesis and catalysis [20]. Industrial applications of iron include the Reppe [21,22] and Haber–Bosch [23] processes where the iron catalysts are used for the large-scale synthesis of alcohols and ammonia, respectively. Due to cheap, easy accessibility, and environmental benign nature, different Fe-catalyzed/mediated organic reactions have been widely developed and applied [24]. Consequently, a number of useful review articles have been published [25–28]. However, limited reviews describe the Fe-catalyzed oxidative coupling reactions and mostly focused to C–C bond formations [27]. Hence, there is an urgent need to review the Fe-catalyzed C–C and C–heteroatom oxidative coupling reactions. Considering this herein we summaries the catalytic applications of iron salts for different C–C and C–heteroatom oxidative coupling reactions. In addition, the present review aims to discuss the recent progress in the step- and atom-economy synthesis of heterocycles, natural products, and bioactive molecules via Fe-catalyzed oxidative annulation reactions.

### C–C Oxidative Coupling

The C–C bond formation is one of the most fundamental topics in organic synthesis. Among different methods, oxidative coupling of two C–H bonds is an efficient, ecofriendly and straightforward method for construction of C–C bonds. Thus, TM-catalyzed coupling reactions starting from two different C–H bonds have received more attention [29,30]. Various late transition metal catalysts have been used for C–C oxidative bond forming reactions [13–18]. In 2007, Li et al. made a significant breakthrough in C–C oxidative coupling reactions using iron catalyst [31]. Later on, different research groups develop a range of Fe-based catalytic systems for C–C bond forming reactions. In this part we review the iron-catalyzed oxidative coupling reactions, and categorized according to the hybridizations of the carbon reaction centers.

#### C(sp<sup>3</sup>)-C(sp<sup>3</sup>) oxidative coupling:

The first example of C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond forming reaction via Fe-catalyzed oxidative coupling was reported by Li et al. [31]. The intermolecular coupling between benzylic derivatives 1 with active dicarbonyl methylene compounds 2 afforded the products 3 in high yields in presence of  $FeCl_2$  as catalyst and di-*tert*-butyl peroxide (DTBP) as oxidant (Scheme 2). Both steric and electronic influences of substrates were investigated under the optimized conditions. The electronic influence did not affect the product yield; however, steric effect decreases the yield. In case of cyclic benzylic derivatives, the desired products were obtained as 1:1 mixture of diastereomers from the reactions with unsymmetrical  $\beta$ -dicarbonyl compounds.

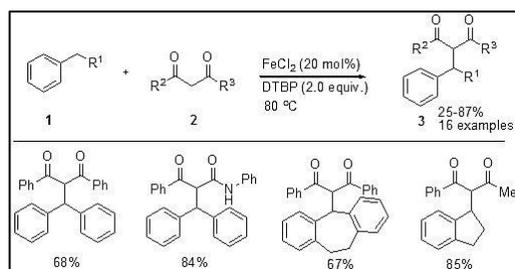


Scheme 2: Fe-catalyzed oxidative coupling between benzylic compounds with 1,3-dicarbonyl compounds

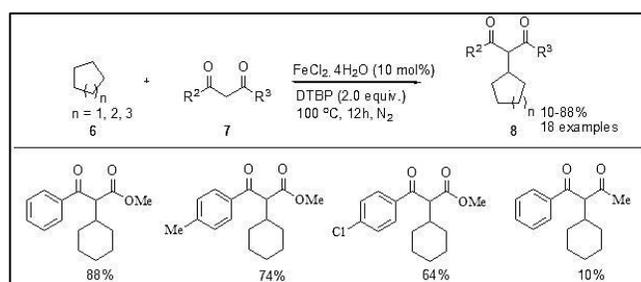
A possible mechanism for the iron-catalyzed C(sp<sup>3</sup>)-C(sp<sup>3</sup>) oxidative coupling between benzylic compounds with 1,3-dicarbonyl compounds is shown in Scheme 3. Initially, DTBP undergoes homolytic cleavage to generate *tert*-butoxyl radical, which react with benzylic derivatives 1 to form the radical 4. Subsequently, 1,3-dicarbonyl

compounds **2** coordinate with Fe(III) to yield intermediate complex **5**. Finally, **4** on radical addition with **5** provided the desired product **3**.

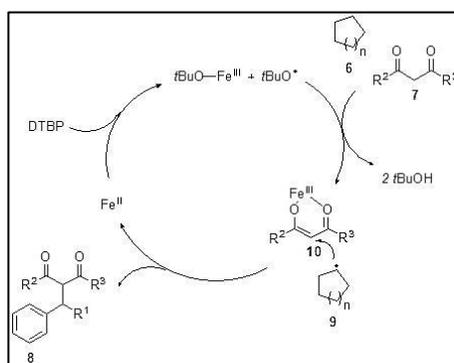
Shortly after, Zhang and Li demonstrated the oxidative coupling between cycloalkanes **6** with activated methylene compounds **7** (Scheme 4) [32]. Among various iron salts, FeCl<sub>2</sub>·4H<sub>2</sub>O exhibited the best efficacy. In presence of DTBP as oxidant the reaction proceeds smoothly at 100°C, affording the products **8** in high yields. Under the optimized conditions, numerous activated methylene compounds were coupled with cyclopentane, cyclohexane, cycloheptane, norbornane, adamantane. With β-keto esters, cycloalkanes were transformed into desired products in high yields. However, reacting with 1,3-diketones decrease the yields. Notably, this is the only successful example on oxidative transformation of the unreactive alkyl C(sp<sup>3</sup>)-H bond into C-C bond employing Fe-catalyst. The mechanism proceeds through the following steps as shown in Scheme 5. In the first step, Fe(II) react with DTBP to give *tert*-butoxyl radical and an <sup>t</sup>Bu-Fe(III). The *tert*-butoxyl radical abstracts hydrogen from cycloalkanes to generate cycloalkyl radical **9**, whereas <sup>t</sup>Bu-Fe(III) make complex with β-keto ester to form Fe-enolate **10**. Finally, radical **9** react with the enolate **10** to afford the desired product **3** and regenerate Fe(II) for subsequent cycle.



Scheme 3: Proposed mechanism for Fe-catalyzed oxidative coupling between benzylic compounds with 1,3-dicarbonyl compounds

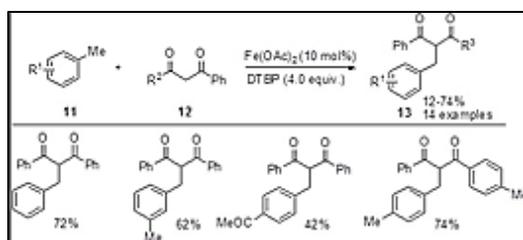


Scheme 4: Fe-catalyzed oxidative coupling between cycloalkanes with 1,3-dicarbonyl compounds



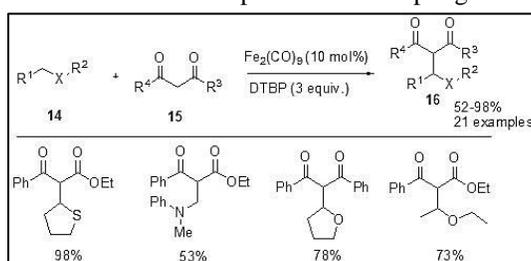
Scheme 5: Proposed mechanism for Fe-catalyzed oxidative coupling between cycloalkanes with 1,3-dicarbonyl compounds

Similar to Li's procedure, ZhiPing et al. described the oxidative coupling between substituted toluenes **11** with 1,3-dicarbonyl compounds **12** in presence of Fe(OAc)<sub>2</sub> as catalyst and DTBP as the oxidant (Scheme 6) [33]. The direct coupling of toluenes with 1,3-dicarbonyl compounds results in the construction of C-benzylated products **13**, and neither the toluenes nor the 1,3-dicarbonyl compounds need to be prefunctionalized.



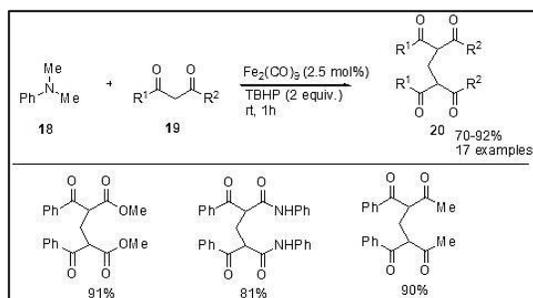
**Scheme 6: Fe-catalyzed oxidative coupling between toluene derivatives with 1,3-dicarbonyl compounds**

Inspired by the success of early investigation on Fe-catalyzed oxidative coupling, Li et al. demonstrated an iron-catalyzed  $C(sp^3)-C(sp^3)$  bond formation by selective coupling of  $\alpha-C(sp^3)-H$  bond of ethers 14 with 1,3-dicarbonyl compounds 15. Among the screened reaction conditions, best results were achieved using  $Fe_2(CO)_9$  as catalyst and DTBP as oxidant. Under the optimized conditions, both acyclic and cyclic ethers coupled with 1,3-dicarbonyl compounds, affording the corresponding products in 12-74% yields. Notably, tetrahydrothiophenes and *N,N*-dimethylanilines were also suitable substrates in this unprecedented coupling reaction (Scheme 7) [34].



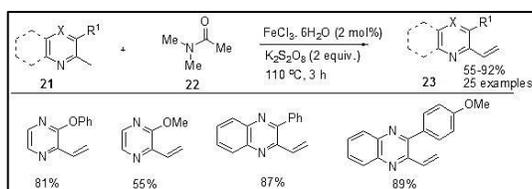
**Scheme 7: Fe-catalyzed oxidative coupling between  $C(sp^3)-H$  bond adjacent to heteroatom with 1,3-dicarbonyl compounds**

In Subsequent studies, they reported an expedite route for the synthesis of methylene bridged bis-1,3-dicarbonyl compounds 20 by using *N,N*-dimethylaniline 18 as the methylene source (Scheme 8) [35]. Reaction of two equivalent of 1,3-dicarbonyl compounds 19 with *N,N*-dimethyl anilines 18 generate good to excellent yields of the product. Among different iron sources,  $Fe_2(CO)_9$  showed high efficacy in combination with *tert*-butyl hydroperoxide (TBHP) as the oxidant.

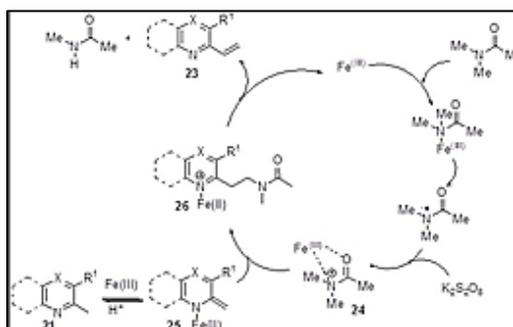


**Scheme 8: Fe-catalyzed oxidative coupling between 1,3-dicarbonyl compounds with *N,N*-dimethyl aniline**

Later, Xu et al. developed a concise route for synthesis of terminal aromatic alkenes via iron-catalyzed vinylation of the benzylic  $C-H$  bond using the *N,N*-dimethyl acetamide (DMA) as the carbon source [36]. Optimization of the reaction indicates  $FeCl_3 \cdot 6H_2O$  is the best catalyst and  $K_2S_2O_8$  as the efficient oxidant (Scheme 9). With optimum conditions, scope of the reaction was evaluated. Azaarenes without any substituents at C-3 position did not couple with DMA, however, C-3 substituted azaarenes generate the terminal olefins in moderate to good yields. Notably, in case of diethyl 2,6-dimethylpyridine-3,5-dicarboxylate, selective vinylation was achieved even on high catalyst loading. Based on preliminary mechanistic investigation by radical scavenger, deuterated experiments and KIE studies, a tentative mechanism was proposed (Scheme 10). First DMA react with Fe(III) to form the iminium species 24. On the other side 21 react with Fe(III) to form the enamine 25. Subsequently, the *in situ* generated enamine 25 react with iminium species 24 to afford the intermediate 26, which then undergoes elimination to generate the desired product 23.



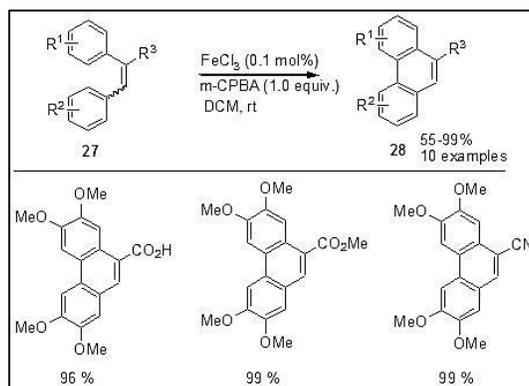
Scheme 9: Fe-catalyzed oxidative coupling between 2-aza arenes with DMA



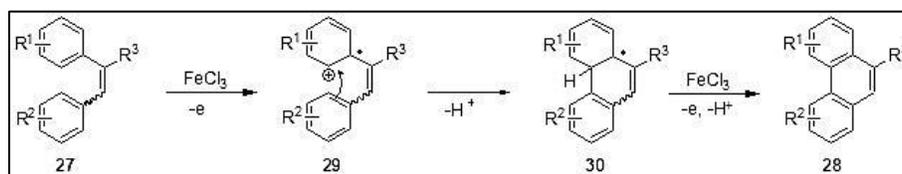
Scheme 10: Proposed mechanism for Fe-catalyzed oxidative coupling between 2-aza arenes with DMA

**C(sp<sup>2</sup>)-C(sp<sup>2</sup>) oxidative coupling**

One of the earliest accounts of C(sp<sup>2</sup>)-C(sp<sup>2</sup>) oxidative-coupling was the contribution of Tobinaga et al. [37]. They described that the oxidative C-C bond formation between phenols with aryl ethers was achieved using iron complex in acetonitrile. However, the importance of Tobinaga's methodology for C-C bond forming reactions could not be realized to its full potential for more than two decades. In 2009, Wang et al. reported  $\text{FeCl}_3$ -catalyzed intramolecular oxidative coupling of 2,3-diarylmethylacrylic acid derivatives **27** using *meta*-chloroperbenzoic acid (*m*-CPBA) as the oxidant [38]. A number of phenanthrene derivatives **28** were synthesized via Fe-catalyzed C(sp<sup>2</sup>)-C(sp<sup>2</sup>) coupling reaction in excellent yields (Scheme 11). Moreover, under the optimized conditions, homo-coupling of 2-naphthols and phenol ethers afforded moderate to good yields of the product (47-76%). A possible mechanism is shown in Scheme 12.



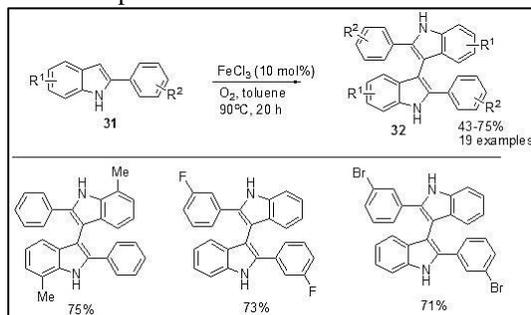
Scheme 11: Fe-catalyzed intramolecular oxidative coupling of 2,3-diarylmethylacrylic acid derivatives



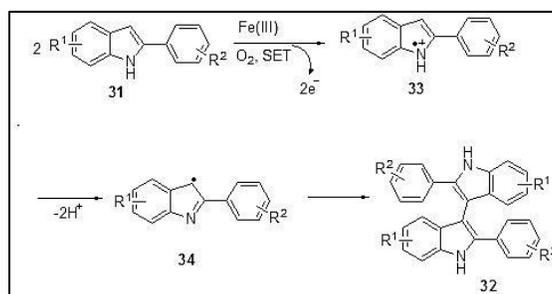
Scheme 12: Proposed mechanism for Fe-catalyzed intramolecular oxidative coupling of 2,3-diarylmethylacrylic acid derivatives

Fe-salts can also be utilized for the oxidative homo-coupling of heteroarenes in presence of suitable oxidant. In this respect, Niu and Zhang demonstrated an efficient and facile route for the synthesis of 3,3'-biindolyls **32** by oxidative homo coupling of aryl indoles **31** [39]. 10 mol% of  $\text{FeCl}_3$  as catalyst and  $\text{O}_2$  as oxidant was found to be the optimum

reaction conditions. The reaction proceeds with both electron-rich, and -deficient 2-aryl indoles and tolerates functional groups such as chloro, bromo and iodo (Scheme 13) They proposed a radical mechanism for the product formation (Scheme 14). The catalytic cycle is initiated by Fe-catalyzed single electron transfer of 2-aryl indoles 31 to form the cation radical species 33 which on deprotonation generate the intermediate radical 34. 34 undergo homo-coupling with another molecule to form the product 32.

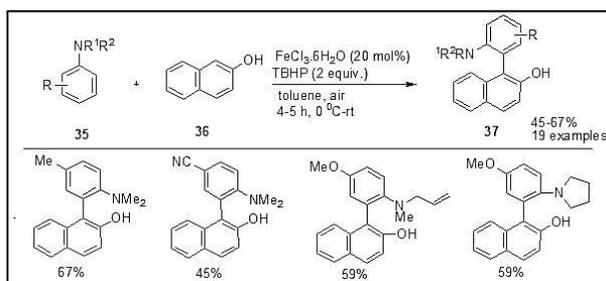


Scheme 13: Fe-catalyzed oxidative homo-coupling of aryl indoles

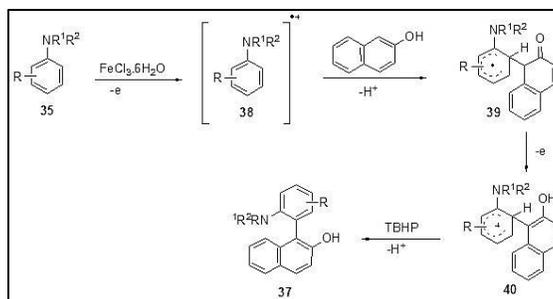


Scheme 14: Proposed mechanism for Fe-catalyzed oxidative homo-coupling of aryl indoles

Later, oxidative coupling between two different arenes were studied by Chandrasekharam et al. Reactions of *N,N*-dialkylanilines 35 with 2-naphthols 36 resulted the desired product 37 in moderate yields in presence of FeCl<sub>3</sub>/TBHP. (Scheme 15) [40]. They proposed a radical mechanism for the product formation as shown in Scheme 16. The catalytic cycle is initiated with the oxidation of aniline derivatives 35 in presence of Fe(III) to form the cation radical 38 and Fe(II). Subsequently, 2-naphthols 36 undergo electrophilic attack on 38 at ortho-position to generate the intermediate 39. With subsequent loss of electron, 39 is converted into 40 which on dehydroaromatization form the final product 37 and the *in situ* generated Fe(II) is oxidized into Fe(III) in presence of TBHP (Scheme 16).

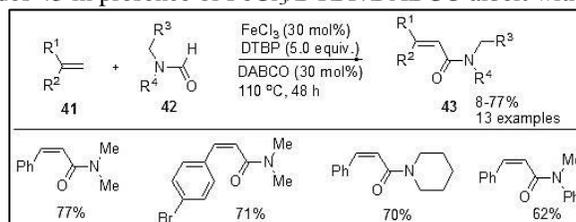


Scheme 15: Fe-catalyzed oxidative coupling between anilines with 2-naphthols



Scheme 16: Proposed mechanism for Fe-catalyzed oxidative coupling between anilines with 2-naphthols

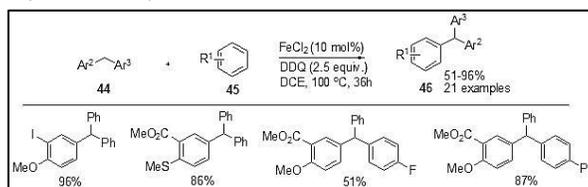
Recently, Li et al. developed a novel and facile method for synthesizing  $\alpha,\beta$ -unsaturated amides 43 by oxidative coupling of unactivated alkenes 41 with formamide derivatives 42 using iron salt [41]. The reaction smoothly generates  $\alpha,\beta$ -unsaturated amides 43 in presence of  $\text{FeCl}_3$ /DTBP/DABCO albeit with moderate yields (Scheme 17).



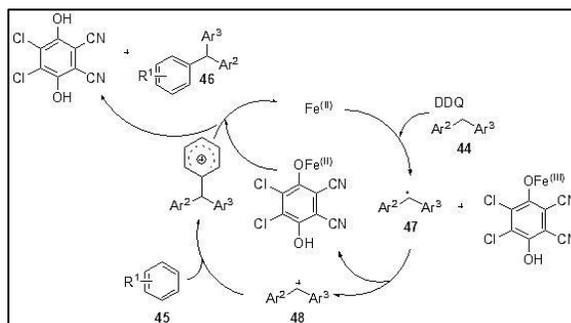
Scheme 17: Fe-catalyzed oxidative coupling of alkenes with amides

### C(sp<sup>2</sup>)-C(sp<sup>3</sup>) oxidative coupling:

On investigating the mechanism of Li's first reported oxidative coupling [31], it was further considered that other nucleophiles may react with the intermediate generated from diphenylmethane derivatives. Based on the above observation, Shi et al. demonstrated an unprecedented Fe-catalyzed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) oxidative coupling between benzylic C-H bonds 44 with electron rich arenes 45 (Scheme 18) [42]. Among the screened catalysts,  $\text{FeCl}_2$  showed high catalytic efficiency in presence of DDQ as the oxidant in dichloroethane. Differently substituted electron rich arenes coupled with diarylmethanes, affording the product 46 with high selectivity. On judicious tuning the electronic properties of the arenes, double oxidative coupling were observed. Initially diaryl methanes 44 undergo iron assisted SET oxidation to form the benzyl radical 47, which further oxidized to the benzyl cation 48. Subsequently, Friedel-Crafts-type processes followed by abstraction of the proton by the reduced hydroquinone generate the desired product 46 (Scheme 19).

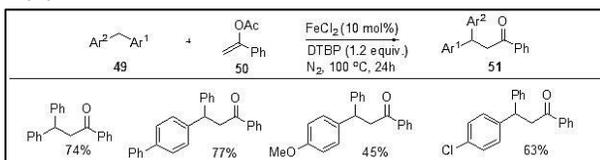


Scheme 18: Fe-catalyzed oxidative coupling between diarylmethanes with arenes



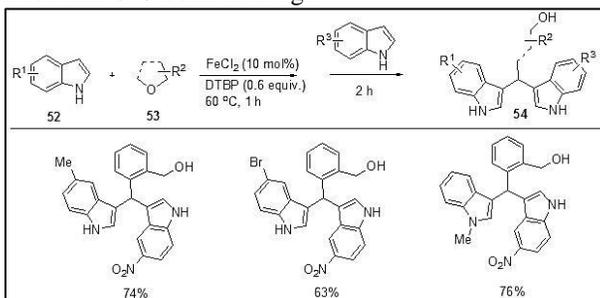
Scheme 19: Proposed mechanism for Fe-catalyzed oxidative coupling between diarylmethanes with arenes

Shortly after, they further studied the oxidative coupling of diarylmethanes 49 with electron rich alkenes 50 [43]. After screening the reaction conditions, they found that FeCl<sub>2</sub> in combination with DTBP as the oxidant afforded the desired product 51 in satisfactory yields (Scheme 20).



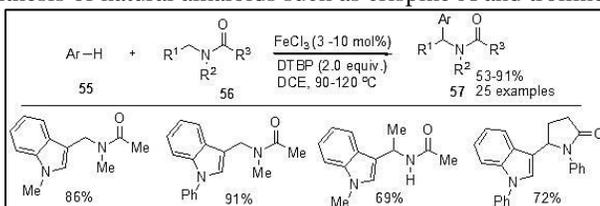
Scheme 20: Fe-catalyzed oxidative coupling between alkenes with diarylmethanes

Besides diarylmethanes, C(sp<sup>3</sup>)-H bond adjacent to heteroatom was also used as the coupling partner for the C(sp<sup>3</sup>)-C(sp<sup>2</sup>) bond forming reactions. In this respect, Li et al. reported Fe-catalyzed oxidative coupling between indoles 52 with ethers 53 (Scheme 21) [44]. In presence of DTBP as the oxidant, the reaction generate 1,1-bis-indolylmethanes 54 via cascade C-H bond oxidation and C-O bond cleavage.

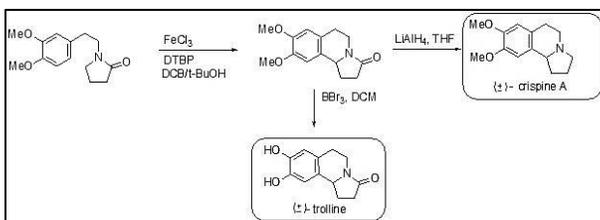


Scheme 21: Fe-catalyzed oxidative coupling between indoles with ethers

Later on, C(sp<sup>3</sup>)-H bond adjacent to nitrogen atom was studied for  $\alpha$ -arylation reactions via Fe-catalyzed oxidative coupling. The reaction ran very smoothly to get the cross-coupled product in good to excellent yields in presence of FeCl<sub>3</sub> and DTBP (Scheme 22) [45]. Under the developed conditions, various electron rich arenes and heteroarenes coupled with alkyl amides, affording the C-arylated product 57. The potential application of the methodology has been demonstrated for the synthesis of natural alkaloids such as crispine A and trolline (Scheme 23) [45].

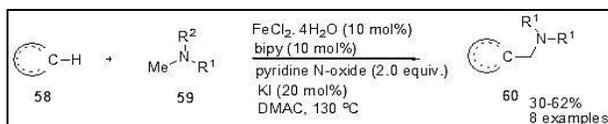


Scheme 22: Fe-catalyzed oxidative coupling between C(sp<sup>3</sup>)-H bond adjacent to nitrogen atom with arenes

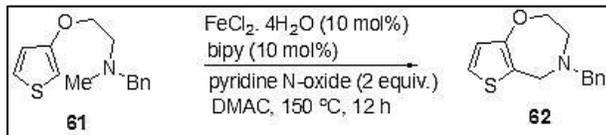


Scheme 23: Total synthesis of Crispine A and Trolline via Fe-catalyzed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) oxidative coupling

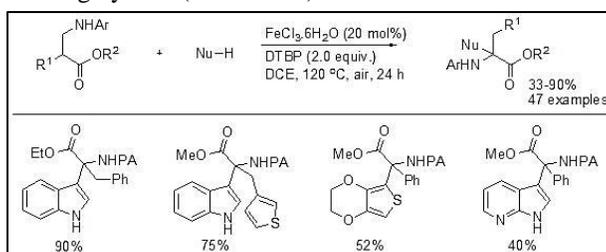
Itami et al. reported the Fe-catalyzed oxidative coupling between electron rich heteroarenes 58 with methyl amine derivatives 59 using pyridine-*N*-oxide as the oxidant (Scheme 24). Using their developed methodology, they synthesized the ligand 62 for the  $\sigma$ 1 receptor protein by intramolecular oxidative coupling of 61 (Scheme 25) [46].



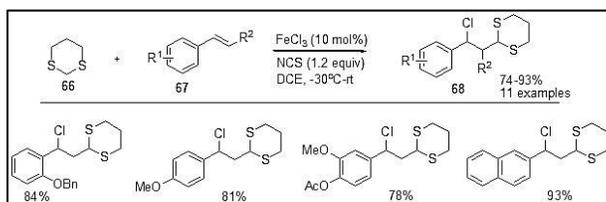
Scheme 24: Fe-catalyzed oxidative coupling between heteroarenes with methylamine derivatives

Scheme 25: Fe-catalyzed synthesis of  $\sigma_1$  receptor ligand

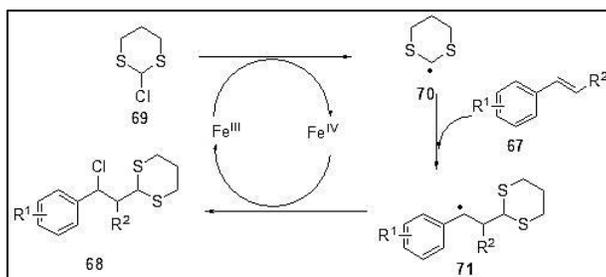
You et al. reported Fe-catalyzed C-C oxidative coupling between arenes with  $\alpha$ -amino acid esters [47]. In presence of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  and DTBP, the reaction proceeds smoothly, generating the  $\alpha$ -quaternary  $\alpha$ -amino acid derivatives 65. Under the optimized conditions, a number of heteroarenes 63 coupled with  $\alpha$ -quaternary  $\alpha$ -amino acid derivatives 64 to afford the desired product 65 in high yields (Scheme 26).

Scheme 26: Fe-catalyzed oxidative coupling between arenes with  $\alpha$ -amino acid esters

Recently, Tang et al. further explored the scope of olefins via iron-catalyzed oxidative coupling between with 1,3-dithianes (Scheme 27) [48]. The reaction afforded good to excellent yields of the product 2-chloro-1,3-dithianes 68 in presence of NCS as the oxidant in DCE. OL-2014-2470. They proposed a radical oxidative coupling pathway for C-C bond forming reactions (Scheme 28). The reaction begins with the formation of chloro derivatives 69 in presence of NCS. 69 undergo Fe-assisted SET oxidation to form 1,3-dithiane radical 70 and chlorine radical. 70 undergo radical addition with alkenes 67 to generate the intermediate 71 which is subsequently trapped by chlorine radical to form the desired product 68.



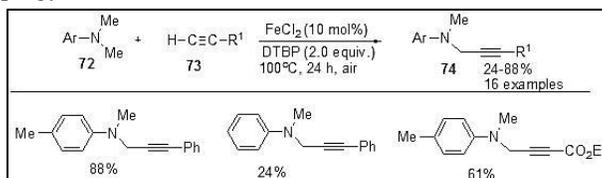
Scheme 27: Fe-catalyzed oxidative coupling between 1,3-dithiane with olefins



Scheme 28: Proposed mechanism for Fe-catalyzed oxidative coupling between 1,3-dithianes with olefins

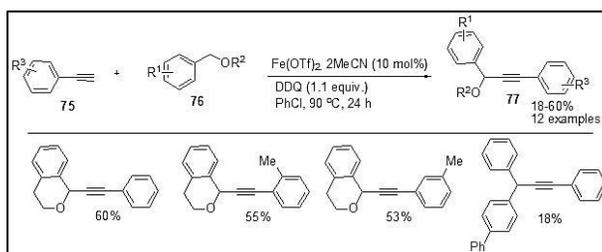
**C(sp)-C(sp<sup>3</sup>) oxidative coupling:**

Unlike other C-C oxidative coupling, limited studies have been done on C(sp)-C(sp<sup>3</sup>) oxidative bond formation. In this context, an impressive example was reported by Volla and Vogel in which tertiary amines **72** were coupled with terminal alkynes **73** under Fe-catalysis (Scheme 29) [49]. After catalyst optimization, FeCl<sub>2</sub> was identified as the best catalyst. In combination with DTBP as oxidant, the desired coupling product **74** was generated smoothly under solvent free conditions. Interestingly two-fold oxidative coupling of alkynes could be possible by silyl protection, affording asymmetric 1,4-propargylic diamines.

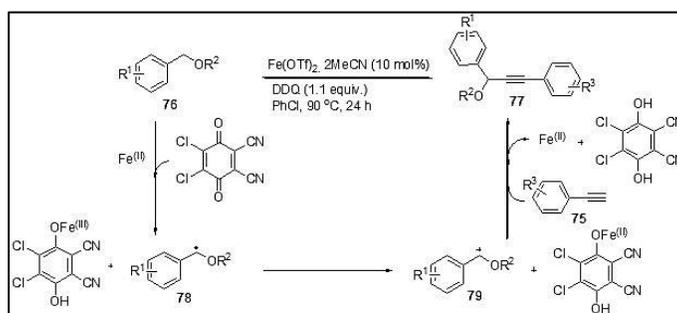


**Scheme 29: Fe-catalyzed oxidative coupling between alkynes with dimethylanilines**

Later on, Jiao et al. developed an Fe-catalyzed oxidative coupling between terminal alkynes with benzylic ethers and alkanes (Scheme 30) [50]. Optimization of the reaction indicate Fe(OTf)<sub>2</sub> in combination with DDQ showed high efficiency towards the C(sp)-C(sp<sup>2</sup>) bond forming reaction. Under the optimized conditions, phenyl acetylene derivatives **75** coupled with benzylic ethers **76** to provide the corresponding product **77** in moderate yields. A possible mechanism is shown in Scheme 31.



**Scheme 30: Fe-catalyzed oxidative coupling between terminal alkynes with benzylic ethers and alkanes**



**Scheme 31: Proposed mechanism for Fe-catalyzed oxidative coupling between terminal alkynes with benzylic ethers and alkanes**

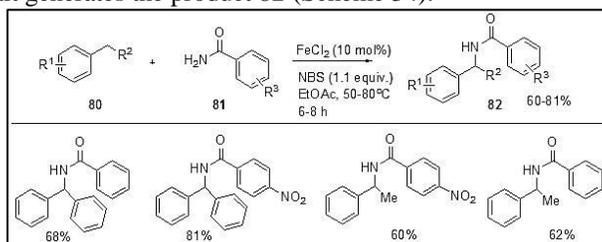
**C-N Oxidative Coupling**

Transition-metal catalyzed oxidative C-N bond formation by coupling different C-H bonds with nitrogen nucleophiles provides a valuable route for synthesizing important nitrogen containing organic compounds [51]. Compared with C-C bond formation; C-N bond formation via oxidative coupling seems more difficult and was reported in recent years.

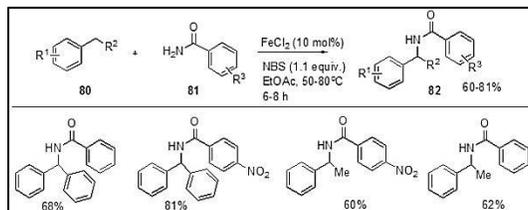
**C(sp<sup>3</sup>)-N oxidative coupling:**

In 2008, Fu et al. first time disclosed the oxidative transformation of C(sp<sup>3</sup>)-H bond into C(sp<sup>3</sup>)-N bond. In their studies they developed an inexpensive, air-stable FeCl<sub>2</sub>/NBS catalyst/oxidant system to efficiently catalyze the amidation of benzylic C(sp<sup>3</sup>)-H bond using carboxamides and sulfonamides as the nitrogen source (Scheme 32) [52]. A possible mechanism for the oxidative amidation of benzylic derivatives was proposed (Scheme 33). Reaction of NBS with amides resulted *N*-bromo amides **83** which on treatment with FeCl<sub>2</sub> gives **84**. Subsequently, **84** is

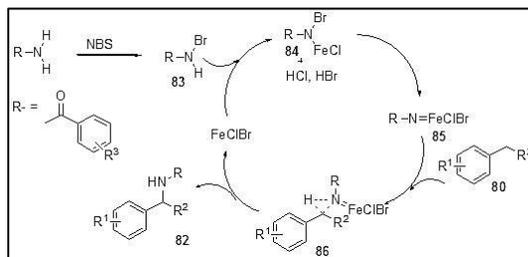
transferred into iron-nitrene complex 85. Reactions of 85 with benzylic derivatives 80 form the intermediate 86 which on elimination of Fe salt generates the product 82 (Scheme 34).



Scheme 32: Fe-catalyzed oxidative coupling between amides with benzyl derivatives

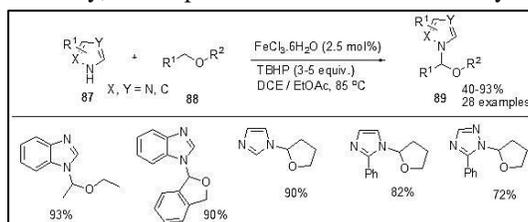


Scheme 33: Fe-catalyzed oxidative coupling between amides with benzyl derivatives

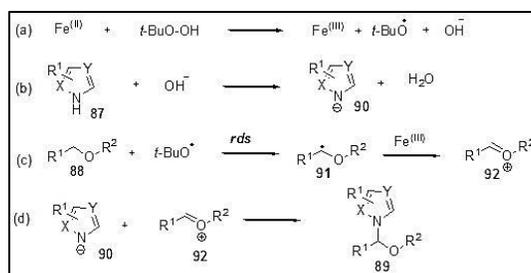


Scheme 34: Proposed mechanism for Fe-catalyzed oxidative coupling between amides with benzyl derivatives

Later, Volla and Vogel described the iron-catalyzed oxidative amidation of C(sp<sup>3</sup>)-H bonds. In their studies, amidation of 4-*N,N*-trimethyl anilines were carried out using benzamide as nitrogen source. In this process, FeCl<sub>2</sub> is proven as the most efficient catalyst and DTBP as oxidant [49]. Inspired by the result on oxidative transformation of C-H bonds adjacent to heteroatom [34], Li et al. disclosed a mild procedure for the *N*-alkylation of azoles via Fe-catalyzed oxidative C-N bond formation. They coupled different azoles 87 with ethers 88. In presence of FeCl<sub>3</sub>·6H<sub>2</sub>O and TBHP, the α-C(sp<sup>3</sup>)-H bond to oxygen in ethers was activated. Numerous imidazoles, and triazoles reacted with ethers, affording the *N*-alkylated product 89 in high yields (Scheme 35) [53]. The mechanism proceeds through the following steps as shown in Scheme 36. In the first step, TBHP cleaves into *tert*-butoxyl radical and hydroxyl anion in presence of Fe(II) catalyst. Hydroxyl ions then react with azoles 87 to generate the anion species 90. *tert*-butoxyl radical abstracts α-hydrogen of ethers 88 to form the intermediate 91 which in presence of Fe(III) transformed into oxonium ions 92. Finally, nucleophilic addition of 90 with 92 yields the desired product 89.

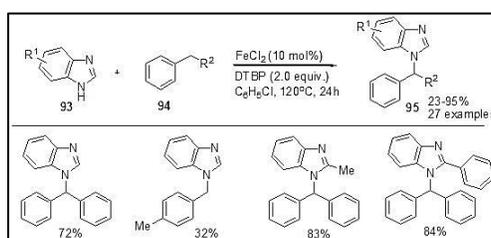


Scheme 35: Fe-catalyzed oxidative coupling between azoles with ethers

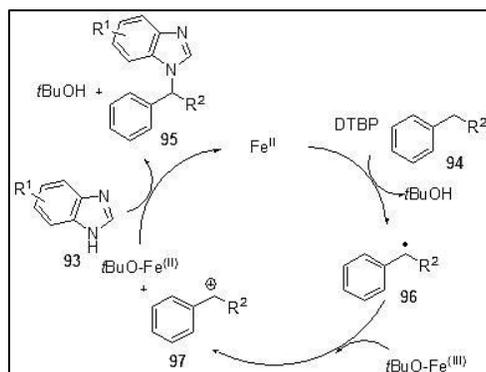


Scheme 36: Proposed mechanism for Fe-catalyzed oxidative coupling between azoles with ethers

In 2011, Chen et al. employed  $\text{FeCl}_2$  as catalyst and DTBP as oxidant for the oxidative C-N bond formation between substituted benzimidazoles 93 with benzylic derivatives 94. Under the optimized conditions, they examined the steric and electronic influence of both the coupling partner (Scheme 37) [54]. A plausible mechanism was proposed (Scheme 38). Diarylmethane undergoes iron assisted SET oxidation to form the benzyl radical 96, which further oxidized to the benzyl cation 97. A subsequent nucleophilic reaction of benzimidazoles 93 with the cations 97 afforded the desired product 95.

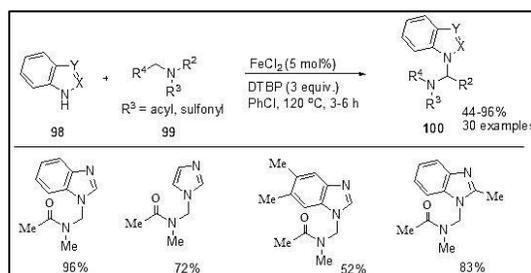


Scheme 37: Fe-catalyzed oxidative coupling between benzimidazoles with benzylic derivatives



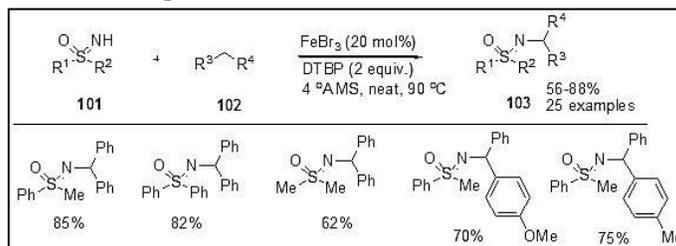
Scheme 38: Proposed mechanism for Fe-catalyzed oxidative coupling between benzimidazoles with benzylic derivatives

In their subsequent studies, azoles derivatives 98 were further investigated for the alkylation reaction (Scheme 39). Screening of the reaction indicated that  $\text{FeCl}_2$  was the best catalyst and DTBP was the most efficient oxidant [55]. They extended their methodology for the oxidative *N*-alkylation of azoles by coupling azoles with amides or sulfonamides.

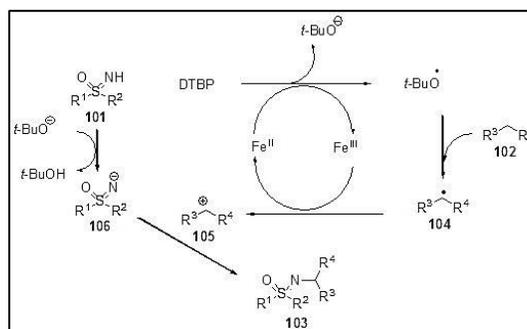


Scheme 39: Fe-catalyzed oxidative coupling between azoles with amides

Recently, Bolm et al. demonstrated Fe-catalyzed oxidative coupling between sulfoximes 101 with diarylmethanes 102 (Scheme 40) [56]. The reaction afforded *N*-alkylated sulfoximes 103 in moderate to good yields under solvent free conditions in presence of DTBP as oxidant. With optimal conditions, they investigated the scope of both sulfoximes and diarylmethanes. The mechanism for the C-N bond forming reaction was proposed in Scheme 41. Initially, DTBP cleaves into *tert*-butoxy anions and *tert*-butoxy radicals in presence of iron (II). The *tert*-butoxy radical then abstract a benzylic hydrogen of 102, affording methylene radical 104, which on SET oxidation forms benzylic cation 105 and Fe(III). 105 reacts with the anion 106 formed by deprotonation of sulfoximes 101 by the *tert*-butoxy anion to generate the desired product 103.



Scheme 40: Fe-catalyzed oxidative coupling between sulfoximes with diarylmethanes



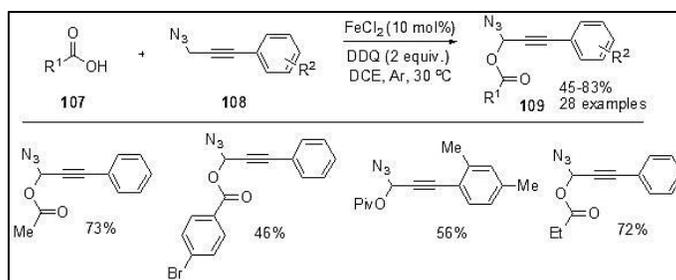
Scheme 41: Proposed mechanism for Fe-catalyzed oxidative coupling between sulfoximes with diarylmethanes

### C-O Oxidative Coupling

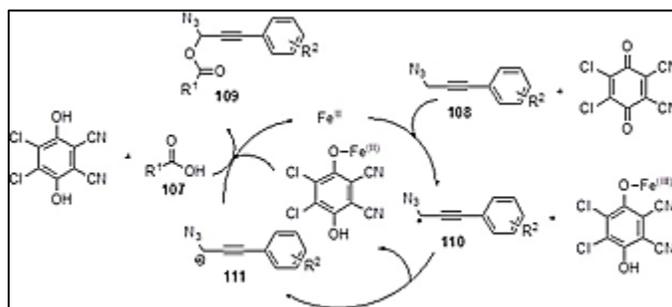
Construction of C-O bonds plays vital role in producing alcohols, ethers, and esters in the synthesis of natural products, drug molecules, and materials [57]. Significant progress has been made in C-O bond formation from carbon-halide bonds, although prefunctionalization of the starting materials was often required and halide containing by-products were formed during the process [58]. Thus, an alternative method involving oxidative coupling between C-H bonds with O-H bonds has received increasing importance from the perspective of atom economy.

### C(sp<sup>3</sup>)-O oxidative coupling:

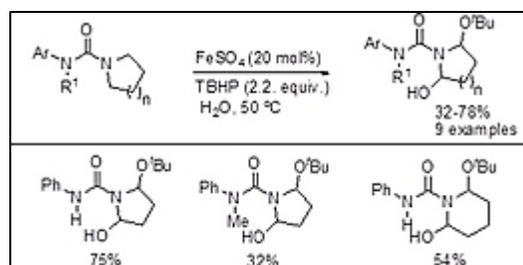
Jiao et al. described iron-catalyzed oxidative C(sp<sup>3</sup>)-O bond formation. In their studies they coupled carboxylic acids 107 with aryl propargyl azides 108 (Scheme 42). Different Iron salts were investigated for the coupling reaction and FeCl<sub>2</sub> showed high catalytic activity [59]. The C-O coupling reaction was performed smoothly using DDQ as oxidant in DCE and affording the product in 45-83% yields. A tentative mechanism for the C-O bond forming reaction is described (Scheme 43). Initially aryl propylazides 108 undergo iron assisted SET oxidation to form the radical 110, which further oxidized to the cation 111. Subsequently, nucleophilic attack by carboxylic acid 107 to cation 111 by carboxylic acid afforded the desired product 109 with the regeneration of the catalyst (Scheme 44).



Scheme 42: Fe-catalyzed C-O oxidative coupling between azides with carboxylic acids

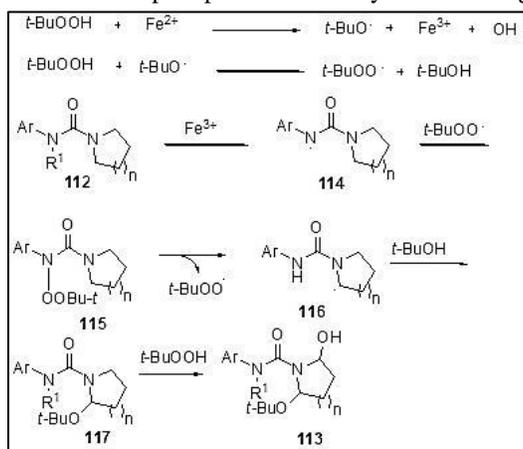


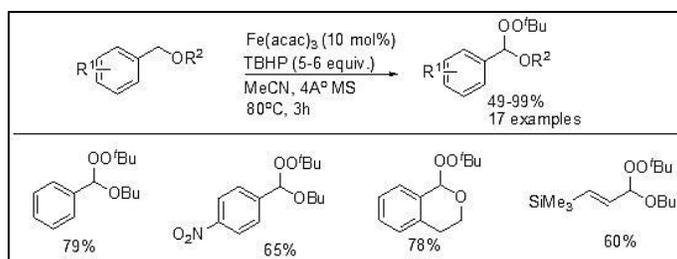
Scheme 43: Proposed mechanism for Fe-catalyzed C-O oxidative coupling between azides with carboxylic acids



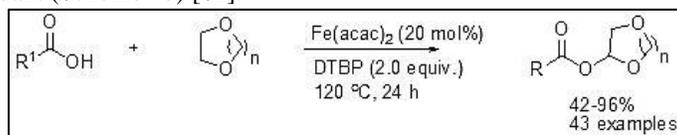
Scheme 44: Fe-catalyzed C-O oxidative coupling

They proposed a radical mechanism for the formation of the product 113 (Scheme 45). Later, Urabe et al. developed the Fe-catalyzed oxygenation reaction for the synthesis of *tert*-butyl peroxyacetals (Scheme 46). Among different iron sources, Fe(acac)<sub>3</sub> was found to be the best catalyst and TBHP as most suitable oxidant in acetonitrile. Under the optimized conditions, a number of C-O coupled products were synthesized in good to excellent yields [60,61].

Scheme 45: Fe-catalyzed C(sp<sup>3</sup>)-O oxidative coupling

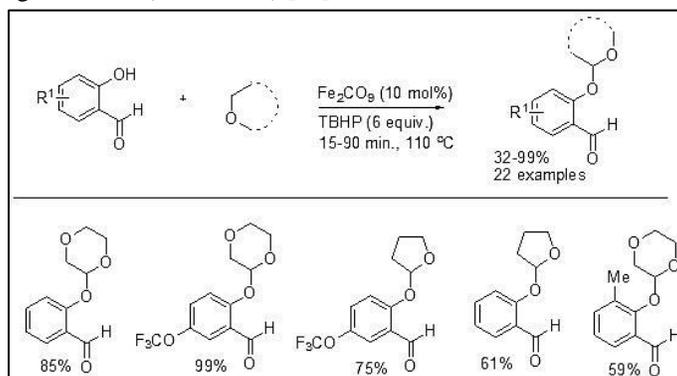
Scheme 46: Fe-catalyzed C(sp<sup>3</sup>)-O oxidative coupling

Recently, Han et al. reported Fe-catalyzed oxidative esterification reaction between carboxylic acids with cyclic ethers using DTBP as oxidant (Scheme 47) [62].

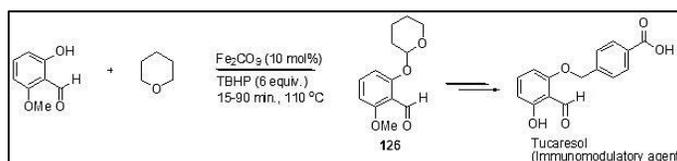


Scheme 47: Fe-catalyzed oxidative coupling between acids with ethers

Chang et al. developed a simple and efficient iron catalyzed selective oxidative C-O bond formation [63]. They coupled salicylaldehyde derivatives 123 with cyclic ethers 124 (Scheme 48). The products were generated smoothly in presence of Fe<sub>2</sub>CO<sub>9</sub>/TBHP. This protocol provides an alternate route for the selective protection of hydroxyl group by ethers. The importance of the methodology is realized by the single step synthesis of key intermediate 126 for immunomodulatory drug, tucaresol (Scheme 49) [64].



Scheme 48: Fe-catalyzed oxidative coupling between salicylaldehydes with cyclic ethers



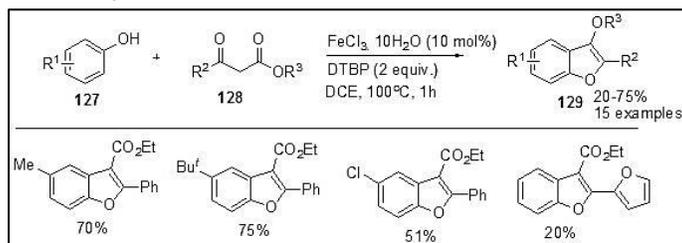
Scheme 49: Potential application of Fe-catalyzed C-O oxidative coupling towards the synthesis of 126

### Oxidative Coupling: Synthesis of Heterocycles

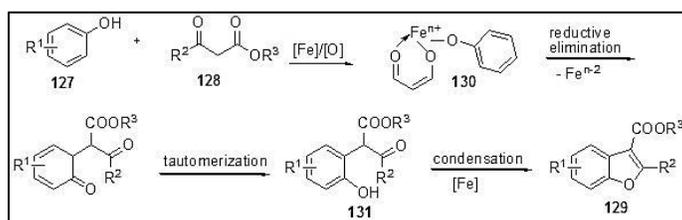
Heterocycles represent an important structural motif found in natural products and drug molecules. The synthesis of heterocycles received paramount attention because of their important biological and physiological activities [65]. Transition-metal catalyzed oxidative coupling is one of the most efficient and convenient method for construction of complex heterocycles from simple substrates, which is considered the ‘holy grail’ of organic chemistry [66]. It provides a step- and atom-economy route for the synthesis of heterocycles. Among the transition metals, use of Fe-catalyst is particularly attractive due to its cheap, non-toxic and eco-friendly nature; features of crucial importance in light of green and sustainable chemistry. Recently, the use of Fe-catalyzed oxidative coupling reactions has gained significant attention, and a range of these methodologies relating to the construction of heterocycles have been

successfully developed. A series of important structural motifs including *N*-heterocycles, *O*-heterocycles, and *N,O*-heterocycles have been synthesized using Fe-catalyzed C-C, C-heteroatom oxidative coupling reactions. Further the importance of the methodology is highlighted towards the synthesis of natural products and bioactive molecules.

The first example on synthesis of heterocycles via Fe-catalyzed oxidative coupling reactions was reported by Li et al. [67]. They coupled phenols 127 with  $\beta$ -ketoesters 128 employing  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  as catalyst. The reaction smoothly generates substituted benzofurans 129 using DTBP as the oxidant in DCE. (Scheme 50) A tentative mechanism is shown in Scheme 51. Initially, phenols and dicarbonyl compounds coordinate with  $\text{Fe}^{\text{III}}$  to form a chelate complex 130. The *in situ* formed complex 130 undergo reductive elimination followed by tautomerization to form 131. Intramolecular condensation of 131 yields the desired benzofuran 129.

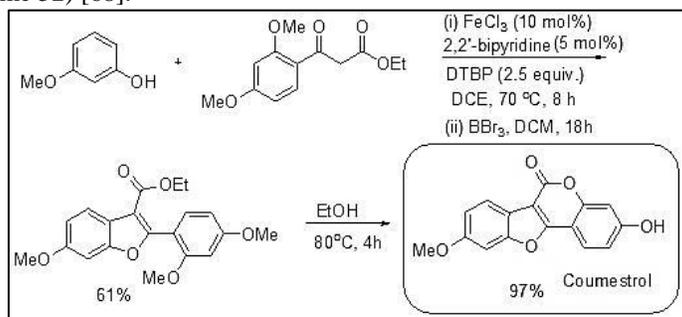


Scheme 50: Fe-catalyzed synthesis of benzofurans



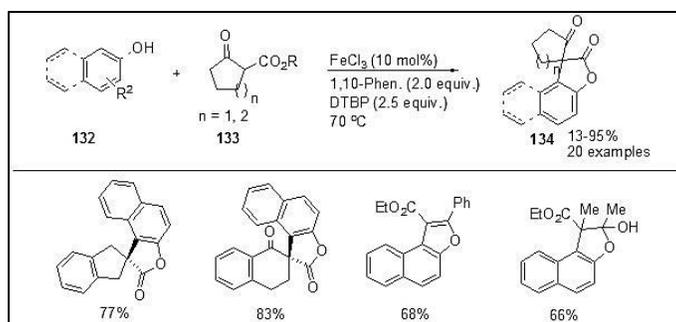
Scheme 51: Proposed mechanism for Fe-catalyzed synthesis of benzofurans

Later, the synthetic utility of the methodology was demonstrated for concise and selective synthesis of natural product coumestrol (Scheme 52) [68].

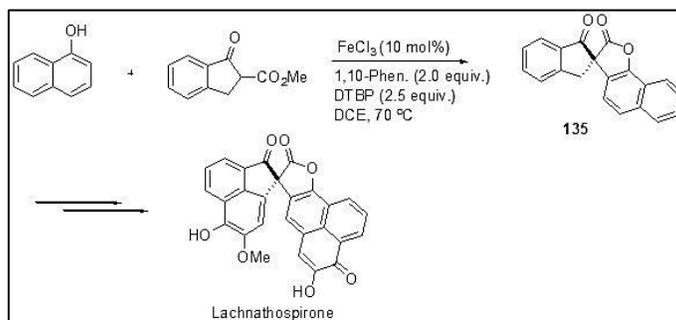


Scheme 52: Fe-catalyzed total synthesis of coumestrol

Later, Pappo et al. introduced ligand in Fe-catalyzed oxidative coupling between phenols 132 with  $\alpha$ -substituted  $\beta$ -keto esters 133. Optimization of the reaction showed  $\text{FeCl}_3$  as the best catalyst. In presence of DTBP as the oxidant and 1,10-phen. as ligand, the coupling reaction afforded the desired polycyclic spirolactones 134 with satisfactory yields (Scheme 53) [69]. The synthetic utility of the above method was applied for the single-step synthesis of spiro compound 135, central core for the natural product lachnanthospirone (Scheme 54).

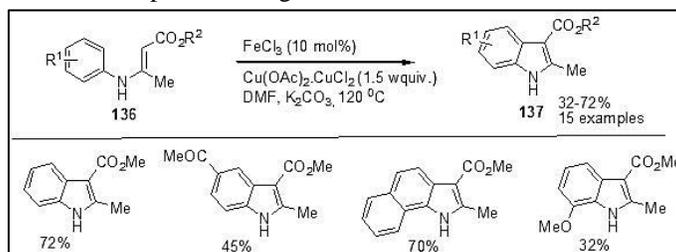


Scheme 53: Fe-catalyzed synthesis of spiroactone

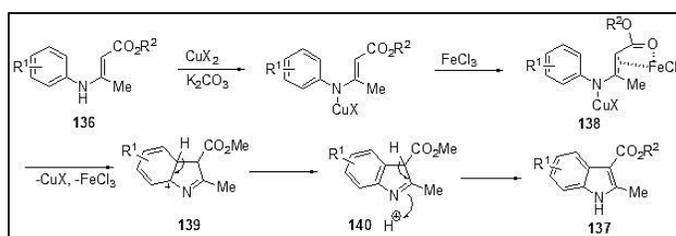


Scheme 54: Fe-catalyzed synthesis of the intermediate 135

Liang et al. reported the synthesis of multi-substituted indoles via Fe-catalyzed  $C(sp^2)$ - $C(sp^2)$  oxidative coupling (Scheme 55). The Fe-catalyzed intramolecular reaction of enamine 136 afforded indole derivatives 137 in moderate to good yields using  $Cu(OAc)_2 \cdot CuCl_2$  as oxidant [70]. Under the optimized condition, they have studied both electronic and steric effect for the cyclization reaction. Arenes having electron-donating group at para position and withdrawing group at ortho-position generate the desired product in high yields. In addition, the cyclization reaction was insensitive to steric hindrance of the substituent on enamine. A tentative mechanism for the cyclization of enamine is shown in Scheme 56. Initially, Enamine 136 on coordination with copper and iron forms the complex 138. The key intermediate 139 is then formed by electrocyclic ring closure of 138. Finally, removal of proton from 139 followed by tautomerization and deprotonation generate the indole derivatives 137.



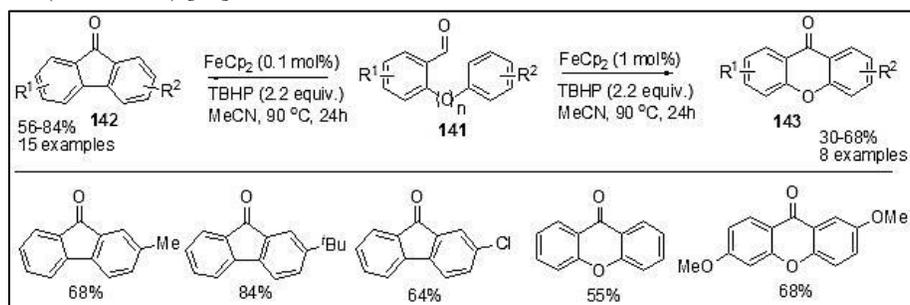
Scheme 55: Fe-catalyzed synthesis of indoles



Scheme 56: Proposed mechanism for Fe-catalyzed synthesis of indoles

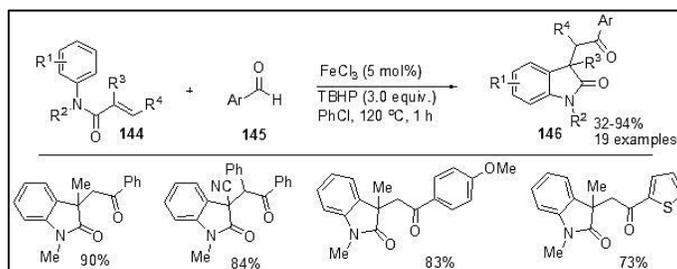
Using the Fe-catalyzed intramolecular  $C(sp^2)$ - $C(sp^2)$  oxidative coupling, Studer et al. developed an efficient method for the synthesis fluorenones and xanthenes. The Fe-catalyzed intramolecular reactions of ortho-formyl biphenyls

and ortho-formyl biphenyl ethers using TBHP as oxidant resulted the corresponding fluorenones 142 and xanthenes 143 in good yields (Scheme 57) [71].

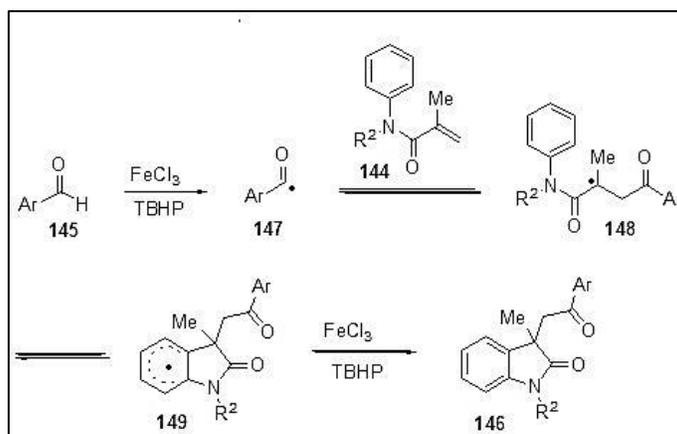


Scheme 57: Fe-catalyzed synthesis of fluorenones and xanthenes

Fe-catalyzed carbonylation-arylation of *N*-arylacrylamides for the synthesis of oxindoles was developed by Li et al. (Scheme 58) [72]. The intermolecular C-C coupling of *N*-methyl-*N*-aryl methacrylamide 144 with aldehydes 145 using  $\text{FeCl}_3$  as catalyst and TBHP as the oxidant provided functionalized oxindoles 146 in good to excellent yields. A possible mechanism for iron-catalyzed carbonylation-arylation of *N*-arylacrylamides is proposed (Scheme 59). In the first step, aldehydes 145 undergo oxidation via SET to form acyl radical 147 in presence of  $\text{FeCl}_3$  and TBHP. Radical addition of 147 to carbon-carbon double bond of 144 results the intermediate 148, which is trapped by a benzenoid  $\Pi$ -system to generate cyclohexadienyl radical 149. Further oxidation of 149 afforded the desired oxindoles 146.

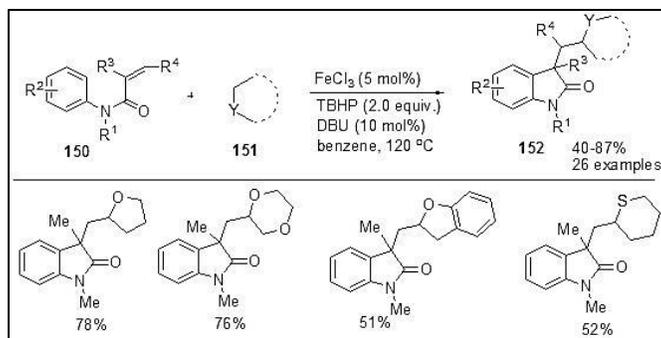


Scheme 58: Fe-catalyzed synthesis of oxindoles



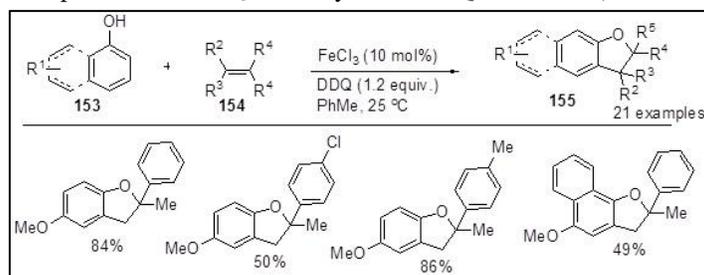
Scheme 59: Proposed mechanism for Fe-catalyzed synthesis of oxindoles

Subsequently, Li et al. developed Fe-catalyzed synthesis of functionalized oxindoles by oxidative C-C bond formation. Among different iron source,  $\text{FeCl}_3$  was the most suitable catalyst for coupling *N*-arylacrylamides 150 having activated alkenes with heteroatom substituted cycloalkanes 151 (Scheme 60) [73]. In presence of TBHP as the oxidant, the reaction afforded good yields of the product 152.



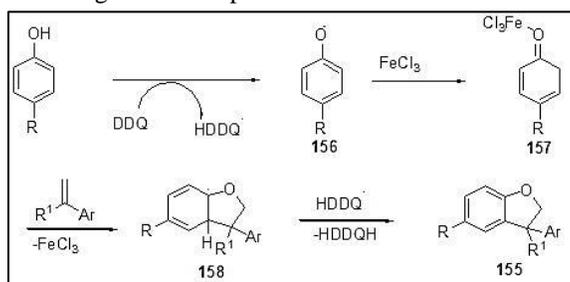
Scheme 60: Fe-catalyzed synthesis of oxindoles

Lei et al. described Fe-catalyzed highly selective oxidative coupling and cyclization between phenols 153 and olefins 154 to construct polysubstituted 2,3-dihydrobenzofurans 155. The coupling reaction generates the desired products 155 in high yields in presence of  $\text{FeCl}_3$  as catalyst and DDQ as oxidant (Scheme 61) [74].



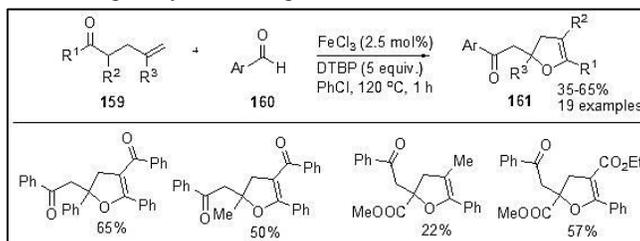
Scheme 61: Fe-catalyzed synthesis of 2,3-dihydrobenzofuran

Based on control experiments, they proposed radical oxidative coupling as shown in Scheme 62. Initially, DDQ oxidizes phenol to HDDQ radical and phenol radical 156. Subsequently 156 is transformed into 157 in presence of  $\text{FeCl}_3$ . In the next step, 156 on radical addition with alkenes 154 form the intermediate 158. Finally, HDDQ radical trapped a hydrogen radical from 158 to generate the product 155.



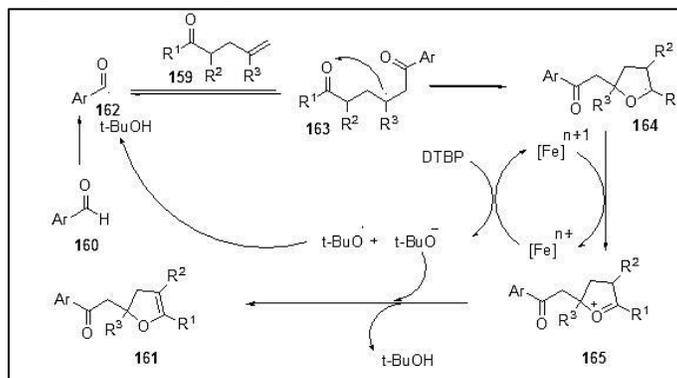
Scheme 62: Proposed mechanism for Fe-catalyzed synthesis of 2,3-dihydrobenzofuran

Very recently, a new synthetic method for the synthesis of functionalized 2,3-dihydrofuran derivatives bearing a quaternary carbon via a Fe-catalyzed acylation-oxygenation of terminal alkenes was described by Li et al. [75]. The Fe-catalyzed oxidative coupling between alkenes bearing  $\gamma$ -carbonyl substituents 159 with aldehydes 160 afforded 2,3-dihydrofurans 161 in moderate to good yields using DTBP as oxidant in chlorobenzene (Scheme 63).



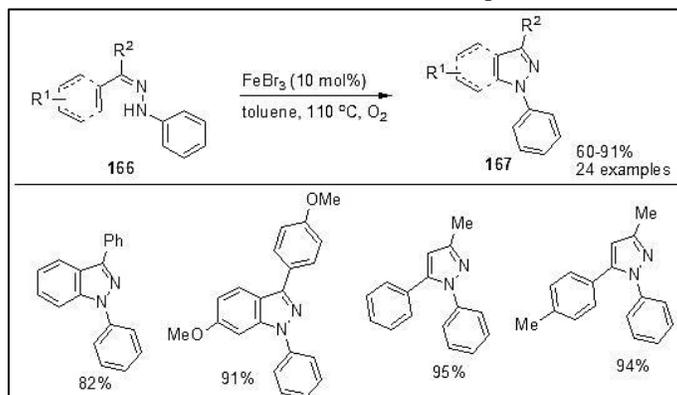
Scheme 63: Fe-catalyzed synthesis of 2,3-dihydrofuran

A plausible mechanism for the iron-catalyzed oxidative acylation oxygenation process is illustrated in Scheme 64. Hydrogen abstraction of aldehyde 160 by *tert*-butoxyl radical afforded acyl radical 162. 162 undergo radical addition with C=C double bond of 159 to form the corresponding carbon radical intermediate 163. 163 on 5-endo-trig radical addition form the intermediate 164. Following iron-catalyzed oxidation, the oxonium cation 165 is generated. The reduced iron catalyst reacts with DTBP to afford *tert*-butoxyl radical along with a *tert*-butoxide anion. Finally, elimination of proton from 165 generates the dihydrofurans 161.

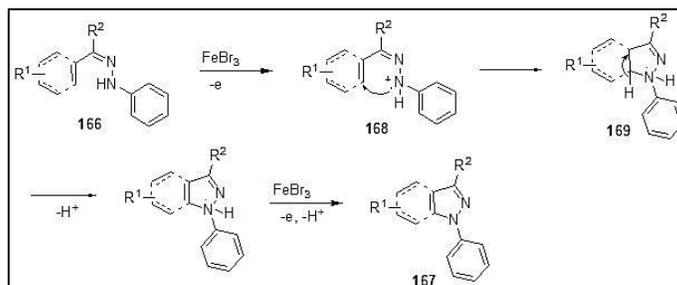


Scheme 64: Proposed mechanism for Fe-catalyzed synthesis of 2,3-dihydrofuran

In 2013, Bao et al. reported intramolecular oxidative amination of aryl hydrazones 166 towards the synthesis of indazoles 167 [76]. They have chosen different iron catalyst for the optimization reactions. The reaction showed high efficiency using  $\text{FeBr}_3$  as catalyst and  $\text{O}_2$  as oxidant (Scheme 65). Under the optimized conditions, they prepared numerous indazoles in good yields. Furthermore, they have synthesized 1,3,5-trisubstituted pyrazoles by intramolecular oxidative coupling of phenylhydrazones. A possible mechanism is proposed in Scheme 66. Aryl hydrazones 166 on oxidation in presence of  $\text{FeBr}_3$  generate the radical cation species 168 and  $\text{Fe(II)}$ . Cation 168 undergo nucleophilic attack by arenes to form the intermediate 169 which on subsequent deprotonation and oxidation generate the product 167.  $\text{Fe(II)}$  is then oxidized to  $\text{Fe(III)}$  in presence of  $\text{O}_2$  and enter into next cycle.

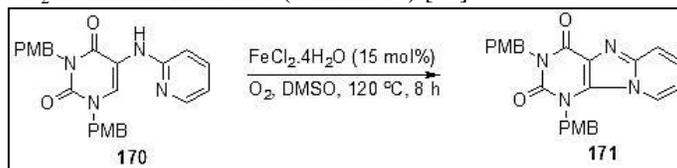


Scheme 65: Fe-catalyzed synthesis of indazoles and pyrazoles



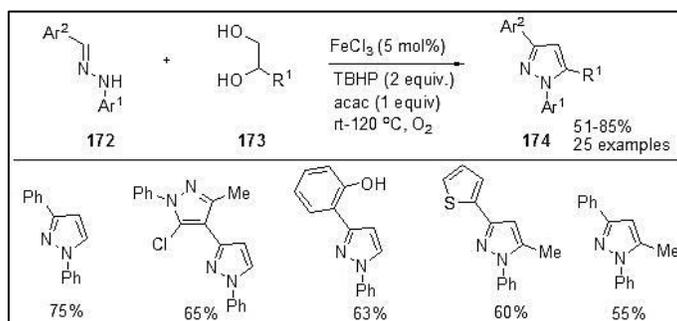
Scheme 66: Proposed mechanism for Fe-catalyzed synthesis of indazoles and pyrazoles

The intramolecular oxidative amination strategy was also applied to 5-(pyridine-2-ylamino)pyrimidine-2,4(1H,3H)-dione 170 for the synthesis of C8-N9 annulated purines 171. The reaction proceeds by employing  $\text{FeCl}_3 \cdot 4\text{H}_2\text{O}$  as catalyst and  $\text{O}_2$  as oxidant in DMSO (Scheme 67) [77].



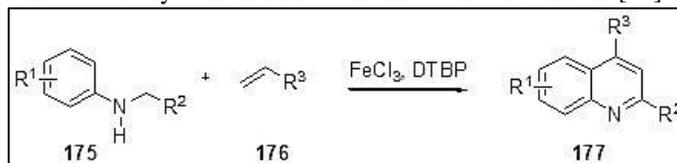
Scheme 67: Fe-catalyzed synthesis of C8-N9 annulated purines

Panda and Jena demonstrated tandem C-C, C-N oxidative coupling and annulation strategy for the synthesis of substituted pyrazoles 174. They disclosed an expedite route for the regioselective synthesis of 1,3-di- and 1,3,5-tri-substituted pyrazoles via Fe-catalyzed oxidative coupling of hydrazones 172 with vicinal diols 173 (Scheme 68) [78]. The reaction generates the desired product smoothly with satisfactory yields in presence of  $\text{FeCl}_3$  as catalyst and TBHP as oxidant in  $\text{O}_2$  atmosphere. Differently substituted pyrazoles were synthesized in moderate to good yields.



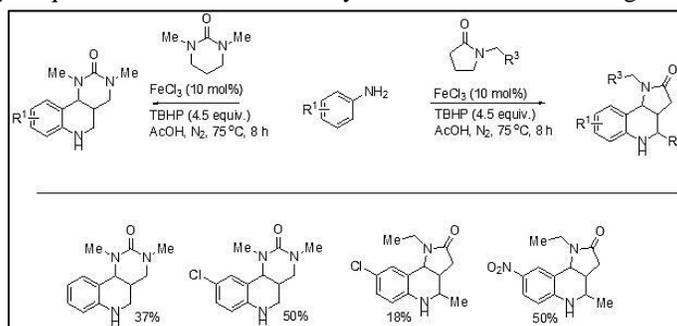
Scheme 68: Fe-catalyzed synthesis of pyrazoles

The tandem C-C and C-N oxidative coupling and cyclization were also applied for the synthesis Quinolines 177 (Scheme 69). Reactions were carried out between *N*-alkylaryl amines 175 with alkenes 176. Optimization of the reaction showed  $\text{FeCl}_3$  was the best catalyst and DTBP as the most suitable oxidant [79].



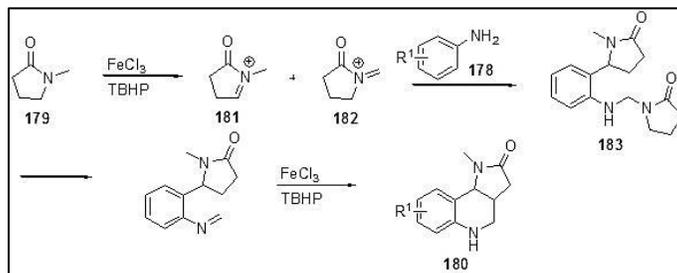
Scheme 69: Fe-catalyzed synthesis of quinolines

Bao et al. demonstrated an unprecedented cyclization between aryl amines 178 with *N*-substituted lactams 179 towards the synthesis of ring fused tetrahydroquinoline derivatives 180 (Scheme 70) [80]. Among the chosen iron source,  $\text{FeCl}_3$  exhibit high catalytic efficiency in presence of TBHP as oxidant. Under the optimized condition, a series of ring fused tetrahydroquinoline derivatives were synthesized in moderate to good yields.



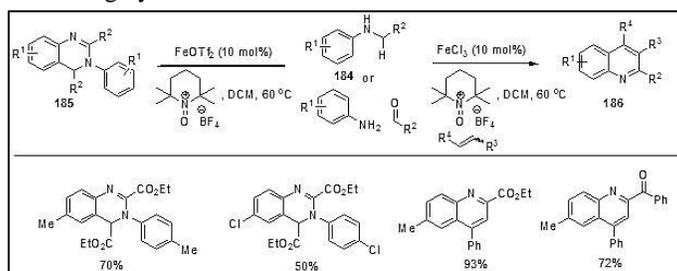
Scheme 70: Fe-catalyzed synthesis of ring fused tetrahydroquinoline

A plausible mechanism is shown in Scheme 71. *N*-substituted lactams undergo oxidation via SET in presence of Fe(III) and TBHP to form the iminium ions 181 and 182. When anilines 178 were added to the reaction mixture, both 181 and 182 reacted with 178 via Friedel–Crafts type reaction and nucleophilic addition reaction respectively to generate the intermediate 183. Subsequently, 183 undergo elimination followed by SET oxidative process to form the product 180.



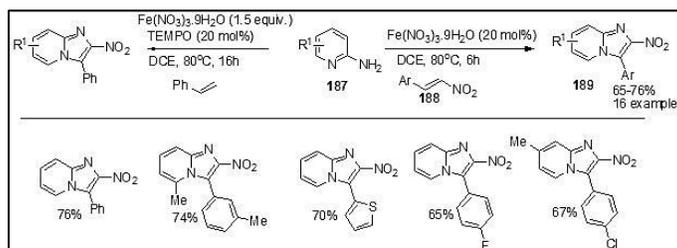
**Scheme 71: Proposed mechanism for Fe-catalyzed synthesis of ring fused tetrahydroquinoline**

Mancheno et al. reported iron-catalyzed oxidative coupling of *N*-alkylanilines 184 towards the divergent synthesis of dihydroquinazolines 185 and quinolines 186 using TEMPO oxoammonium salt as a mild and nontoxic oxidant (Scheme 72) [81]. Fe(OTf)<sub>2</sub> was the most suitable catalyst for the synthesis of dihydroquinazolines, however, FeCl<sub>3</sub> as catalyst afforded quinolines in high yields.

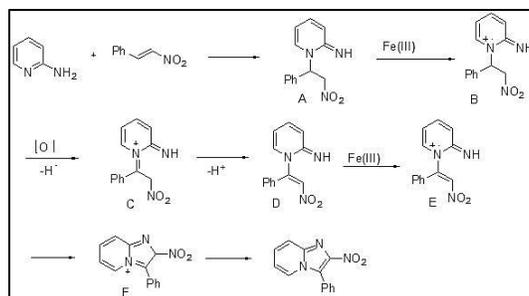


**Scheme 72: Fe-catalyzed synthesis of dihydroquinazolines and quinolines**

Recently, Hazra et al. developed iron-facilitated oxidative diamination procedure towards the regioselective synthesis of functionalized imidazopyridine derivatives 189 (Scheme 73) [82]. They coupled 2-aminopyridines 187 with nitroalkenes 188 in ambient air. The reaction also proceeds by reacting 2-aminopyridines with styrenes. However, the later reaction requires TEMPO as the additional oxidant. They proposed the following possible mechanism as shown in Scheme 74. It involves the Michael addition of 2-amino pyridines 187 with nitroalkanes 188 to form the adduct 190. 190 undergo oxidation by Fe(NO<sub>3</sub>)<sub>3</sub> through SET followed by cyclization and deprotonation generate the desired product 189.

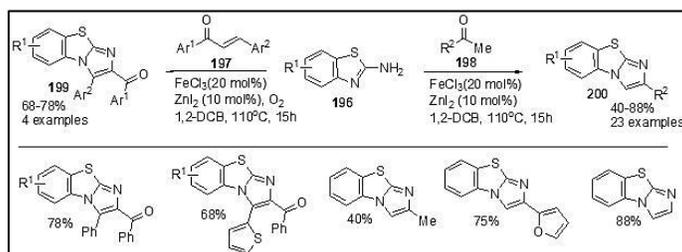
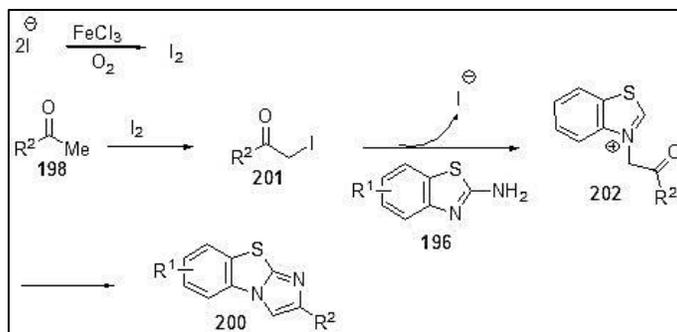


**Scheme 73: Fe-catalyzed synthesis of imidazopyridine**

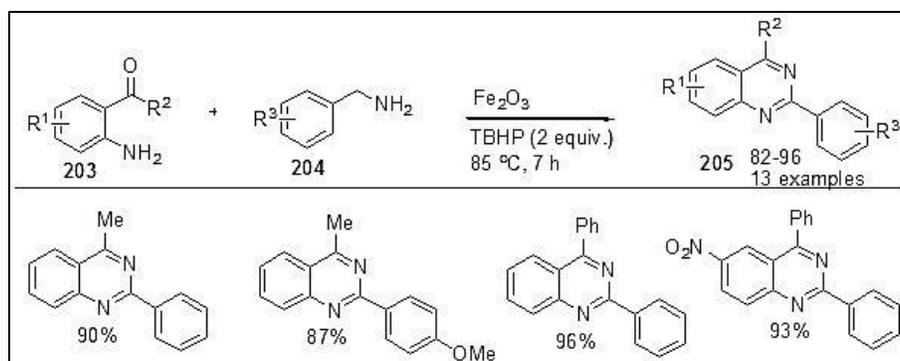


Scheme 74: Proposed mechanism for Fe-catalyzed synthesis of imidazopyridine

Subsequently, they reported oxidative annulations of 2-aminobenzothiazoles 196 with olefins 197 and ketones 198 for synthesis of benzo(*d*)imidazo(2,1-*b*)thiazole 199 and 200 utilizing  $\text{FeCl}_3/\text{ZnI}_2$  as catalyst and  $\text{O}_2$  as oxidant (Scheme 75) [83]. A possible mechanism for the reaction is shown in Scheme 76. The first step involves the generation of iodine by oxidation of iodide anion with aerobic oxygen in the presence of  $\text{FeCl}_3$ . In the subsequent step,  $\alpha$ -iodo ketones 201 is formed by reaction of *in situ* generated iodine with ketones 198. The 2-aminobenzothiazoles 196 react with  $\alpha$ -iodo ketones 201 to form the intermediate 202, which on cyclization afford benzo(*d*)imidazo(2,1-*b*)thiazole 200.

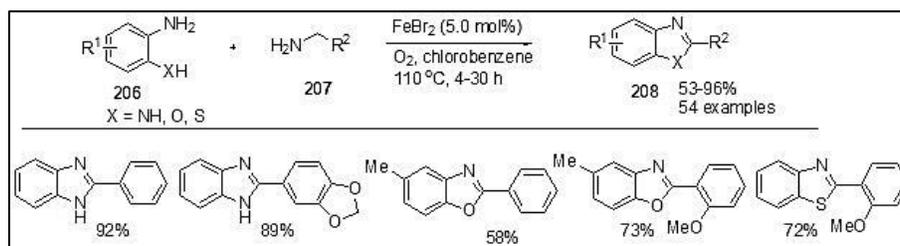
Scheme 75: Fe-catalyzed synthesis of benzo(*d*)imidazo(2,1-*b*)thiazolesScheme 76: Proposed mechanism for Fe-catalyzed synthesis of benzo(*d*)imidazo(2,1-*b*)thiazole

Burri et al. for the first time explored the high surface area and highly reactive magnetic nanocatalyst  $\gamma\text{-Fe}_2\text{O}_3$  towards the oxidative cyclization of 2-aminoarylketones 203 with benzyl amines 204 (Scheme 77). In presence of TBHP as oxidant, the coupling reaction afforded 2-arylquinazolines 205 in excellent yields [84].

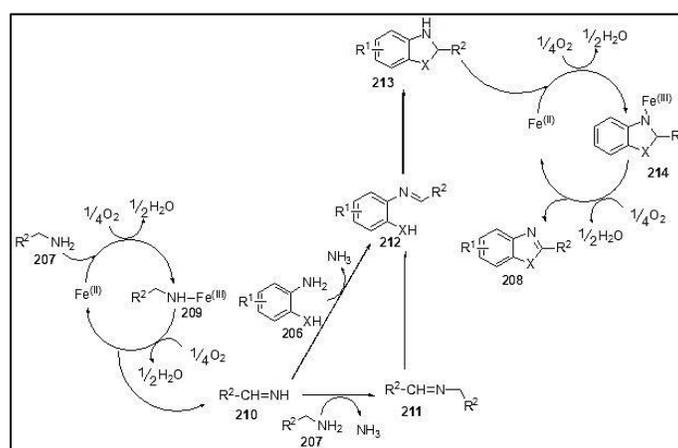


Scheme 77: Fe-catalyzed synthesis of 2-phenylquinazolines

Very recently, Gopalaiah and Chandrudu further expanded the scope of the benzyl amines towards the synthesis of a variety of 1,3-benzazoles via Fe-catalyzed oxidative C-C, C-hetero coupling reactions. Coupling between benzylamines with 2-amino/hydroxy/mercapto-anilines generate the desired substituted benzoxazoles, benzimidazoles, benzthiazoles in moderate to excellent yields in presence of molecular oxygen (Scheme 78) [85]. A proposed mechanism for this reaction is shown in Scheme 79. It involves oxidative addition of iron into benzylamines 207, forming the complex 209, which undergo further oxidation to form benzylimines 210 and generated iron(II)bromide. Imines 210 react with another molecule of benzylamine afforded *N*-benzylbenzaldimines 211 and liberate ammonia. The imines 211 on transimination with 2-amino/hydroxy/mercapto anilines form 2-(benzylideneamino)aniline/phenol/thiophenols 212. In parallel, benzylimines 210 by transimination with 2-amino/hydroxy/mercaptoanilines generate the imines 212 directly. Subsequently, the imines 212 undergo intramolecular cyclization to afford 2-phenyl-2,3-dihydro-1H-benzo(d)imidazole/oxazole/thiazole 213. Oxidation of 213 in the presence of iron(II) bromide and oxygen generate the desired product 208 through the formation of iron complex 214.



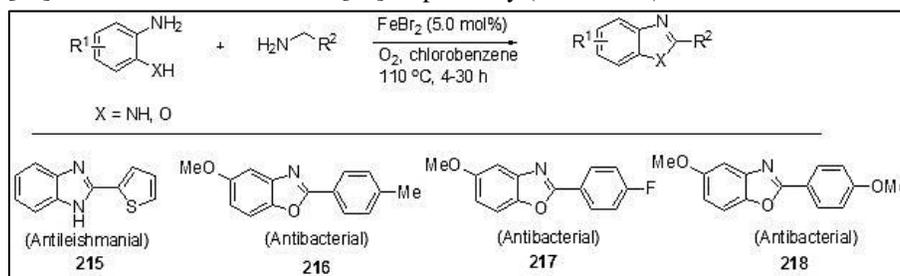
Scheme 78: Fe-catalyzed synthesis of 1,3-benzazoles



Scheme 79: Proposed mechanism for Fe-catalyzed synthesis of 1,3-benzazoles

The synthetic utility of the above methodology has been demonstrated for the direct synthesis of bioactive heterocycles such as 2-(thiophen-2-yl)-1H-benzo(d)imidazole 215, 5-methoxy-2-p-tolylbenzo(d)oxazole 216, 2-(4-

fluorophenyl)-5-methoxybenzo(*d*)oxazole 217, 5-methoxy-2-(4-methoxy)benzo(*d*)oxazole 217 which exhibits antileishmanial [86] and antibacterial activities [87] respectively (Scheme 80).



Scheme 80: Fe-catalyzed synthesis of 215, 216, 217 and 218

## CONCLUSION AND FUTURE CHALLENGES

This review has summarized different types of oxidative coupling reactions between C-H/C-H and C-H/X-H bonds. It also demonstrates the potential application of oxidative annulation strategy towards the step-economy synthesis of drug molecules, bioactive natural products and heterocycles. Significant progress concerning the oxidative C(sp<sup>2</sup>)-C(sp<sup>2</sup>), C(sp<sup>3</sup>)-C(sp<sup>3</sup>), C(sp<sup>2</sup>)-C(sp<sup>3</sup>), C(sp<sup>3</sup>)-N and C(sp<sup>3</sup>)-O bond forming reactions have been achieved. Even so, several new frontiers still exist for further research in oxidative coupling reactions which can be addressed in the following points. (1) Development of mild and efficient Fe-based catalytic system for the oxidative C(sp)-C(sp<sup>3</sup>), C(sp)-N, C(sp<sup>2</sup>)-N, C(sp)-O, C(sp<sup>2</sup>)-O bond forming reactions. (2) Most of the oxidative coupling reactions require expensive and sensitive oxidants such as TBHP, and DTBP. Thus, use of cheap and easily accessible molecular oxygen as the oxidant is highly desirable in context of green chemistry. (3) The C-H bonds are stable and quite unreactive in nature. Although Fe-catalyst plays crucial role for oxidative transformation of C-H bonds into C-C and C-heteroatom bonds, still there is high demand for development of more reactive Fe-based catalytic system with lower catalyst loading. (4) Limited investigations have been done on oxidative coupling reactions of unactivated alkanes. Hence, greater expansion in this area of research is still needed. (5) The mechanism of most Fe-catalyzed oxidative coupling reactions are unclear. Thus, detailed mechanistic investigation is required to promote the discovery of efficient and highly selective catalytic systems. (6) Organic molecules contain numerous C-H bonds with different chemical environment. The chemo- and regio-selective oxidative coupling of target C-H bond leaving other C-H bonds undisturbed is a challenging task.

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