

## Direct C–H Transformation via Iron Catalysis

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## 1. INTRODUCTION

The development and application of efficient, convenient, selective, and environmentally benign synthetic methods is highly desirable in organic chemistry. With this requirement, numerous catalytic processes, especially transition metal-catalyzed processes, have been developed and played vital roles in the syntheses of natural and unnatural compounds. In the last few decades, late transition metal catalysts, such as palladium,<sup>1</sup> ruthenium,<sup>2</sup> rhodium,<sup>3</sup> iridium,<sup>4</sup> gold,<sup>5</sup> and platinum,<sup>6</sup> have exhibited powerful catalytic ability. However, the relatively high price and considerable toxicity limited their applications and possible improvements. Therefore, more and more chemists shifted their attention to the first-row transition metals, especially copper and iron, which own obvious advantages and unique features.

Iron is one of the most important metals in nature, which is closely related to the life of the human being.<sup>7</sup> In nature, iron is the most abundant transition metal and plays a very important role in the life reactivity as well as in the human body as a “king metal”, which showed its magical catalytic ability to facilitate many bioactivities.<sup>8</sup> The application of iron in human history can be traced back to ancient times. Initiated from the mining of the

ferrolite, the study of iron is also one of the oldest fields in chemistry. Iron is also one of the metals which has been early and successfully used in constructing organic compounds. Since then, the development of iron chemistry in organic synthesis has never been stopped due to its advances and significance. The studies in this field have been well reviewed in different aspects in the past several decades. To date, many chemists have made significant contributions in this field, and various iron-catalyzed organic transformations have been realized,<sup>9</sup> including nucleophilic additions, substitutions, reductions, oxidations, hydrogenations, cycloadditions, isomerizations, rearrangements, as well as polymerizations.

Direct C–H transformation has attracted continuous interest since the early 1970s because it meets not only the efficient and sustainable requirement of organic transformations but also the understanding of the intrinsic features of the broadly existing C–H bonds in organic molecules, for example, their accessibility, activity, and selectivity.<sup>10</sup> In the previous studies, the precious late transition metals, for example, Pd,<sup>11</sup> Ir,<sup>12</sup> Rh,<sup>13</sup> Pt,<sup>14</sup> etc.,<sup>15</sup> have been proved to play key roles to facilitate highly efficient transformations through C–H activation. Actually, iron-containing enzyme-catalyzed C–H transformation has been reported and suggested a potential application of iron catalysis in C–H transformation.<sup>16</sup> Combining the advantages of both iron chemistry and C–H transformation, the significance of iron-catalyzed C–H transformations has stimulated rapid development in the past several years. Since Bolm and co-workers significantly summarized the achievements in iron-catalyzed reactions in organic synthesis in 2004,<sup>9</sup> and also other reviews on recent advances of iron chemistry have been published,<sup>17</sup> this review gives a compiled analysis and discussion of advances in iron-catalyzed C–H transformations in the past decade.

## 2. C–H BOND OXIDATION

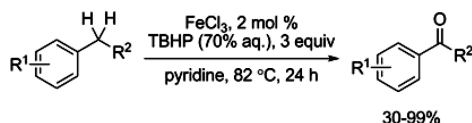
C–H bond oxidation is one of the most common processes in nature. Among the C–H oxidation transformations existing in nature, various transition-metal-containing domains of the enzymes show their high catalytic abilities, in which the single electron transfer (SET) process is considered as a possible pathway to facilitate the C–H oxidation.<sup>18</sup> In general, Fe and Cu, as the “king” of the metals, were found to process these magic transformations in enzymes. In the synthetic field, iron-catalyzed systems for C–H oxidation can be traced back to one century

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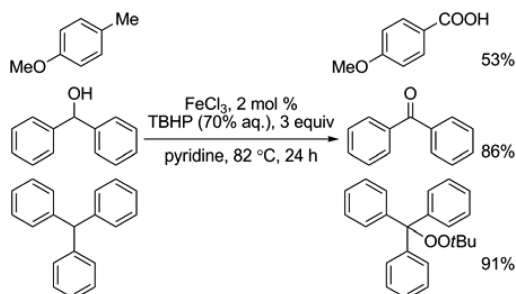
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Scheme 1. Iron-Catalyzed Benzylic Oxidation



Scheme 2. Iron-Catalyzed Oxidation of Benzyl Compounds



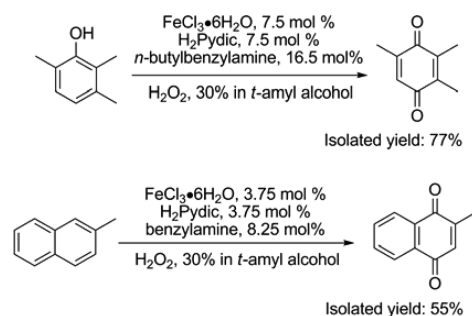
ago, and this was summarized as Gif chemistry<sup>19</sup> and Fenton chemistry,<sup>20</sup> as well as other non-heme mimic systems.<sup>21</sup> Recently, iron-catalyzed oxidation was mostly focused on sulfide oxidations,<sup>22</sup> epoxidation,<sup>23</sup> and olefin dihydroxylation.<sup>23h,24</sup> In contrast, iron-catalyzed C–H bond oxidation has had few significant breakthroughs for a rather long time, until recent years.

In 2007, Bolm and co-workers reported an alternative oxidation protocol, which realized an efficient oxidation of benzylic compounds to carbonyl derivatives under mild reaction conditions.<sup>25</sup> This transformation was clean and efficient using TBHP aqueous solution as the oxidant. Various benzyl compounds were subjected to the optimized condition, and the corresponding carbonyl derivatives were obtained in good to excellent yields (Scheme 1). Furthermore, when 4-methylanisole and diphenylmethanol were subjected to this transformation, the corresponding products 4-methoxybenzoic acid and benzophenone were obtained in high yields, respectively. Unexpectedly, the oxidation of triphenylmethane afforded *tert*-butyl triphenylmethylether (in 91% yield) instead of the corresponding alcohol (Scheme 2).

Besides the direct hydroxylation of benzyl sp<sup>3</sup> C–H bond, iron-catalyzed selective oxidation of the sp<sup>2</sup> C–H bond of phenols and arenes was developed by Beller and co-workers in 2010.<sup>26</sup> A three component catalyst system consisting of FeCl<sub>3</sub>·6H<sub>2</sub>O, pyridine-2,6-dicarboxylic acid (H<sub>2</sub>pydic), and different benzylamines was used for the oxidation of 2,3,6-trimethylphenol (TMP) with hydrogen peroxide, a “green” and nontoxic oxidant. Under the optimized conditions, the oxidations of TMP and 2-methylnaphthalene took place in 77% and 55% isolated yield, respectively (Scheme 3). It is noteworthy that the oxidation product of 2-methylnaphthalene was menadione (namely vitamin K<sub>3</sub>, menaphthone), which served as a precursor to various derivatives of vitamin K. Indeed, such an oxidation toward vitamin K<sub>3</sub> was regarded as an industrially important benchmark system.<sup>27</sup>

Other than the relatively activated benzylic C–H bonds, the oxidation of unactivated alkane sp<sup>3</sup> C–H bonds is more attractive and challenging. From the aged Gif chemistry and Fenton

Scheme 3. Iron-Catalyzed Oxidations of TMP and 2-Methylnaphthalene

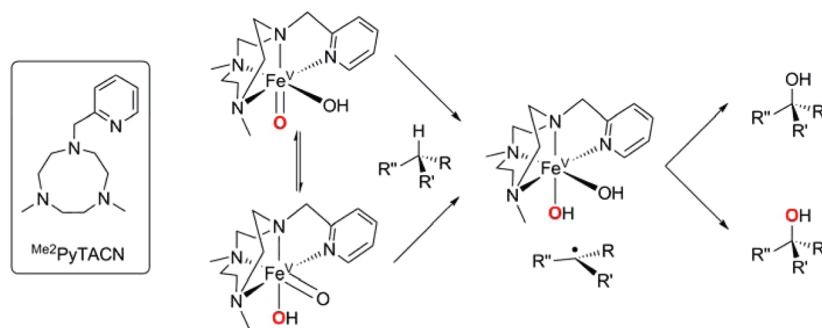


chemistry to modern non-heme mimic systems, highly chemo-selective and efficient alkane C–H oxidation/hydroxylation is always considered as a terminal goal. Nowadays, the improvements focused on the development of synthetic models, using a “green” oxidant such as oxygen, air, or some hyperoxides. Naturally occurring iron- or copper-containing metalloenzymes provide us good examples. Que Jr. has contributed much in the non-heme systems and built up a mechanistic frame to understand metal-centered C–H hydroxylations in non-heme systems, and that, to some extent, provided a theoretical guideline and inspirational suggestion for the following breakthroughs in the use of iron complexes as selective C–H oxidation catalysts. In 1997, Que Jr. reported the first example of a non-heme iron catalyst/H<sub>2</sub>O<sub>2</sub> combination capable of stereospecific alkane hydroxylation.<sup>28</sup> As initiating studies, the use of multidentate nitrogen-containing ligand TPA (tris(2-methylpyridyl)amine) stimulated the following successful development of multidentate nitrogen ligands. Later investigation indicated that iron catalysts bearing multidentate nitrogen ligands provided excellent reactivity. Through the modification of the electronic and steric properties of the multidentate ligands, the catalytic reactivity could be significantly improved.<sup>29</sup> In the meanwhile, Britovsek reported a series of valuable investigations on the synthesis, structural characterization, topological variation, and catalytic application of the tripodal tetradentate nitrogen ligands as well as the corresponding non-heme iron(II) complexes.<sup>30</sup> Nowadays, the design and modification of multidentate nitrogen ligands is becoming more and more popular and crucial for the non-heme iron catalytic system to approach direct C–H transformations.

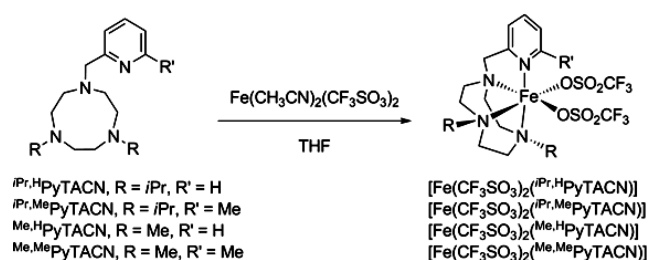
Actually, it was been well proven that a high-valent iron-oxo species could also be accessed by a non-heme ligand environment. A relative mechanism investigation on how the iron-oxo species formed and reacted was also carried out.<sup>29</sup> Non-heme iron enzymes, such as methane monooxygenase<sup>31</sup> and Rieske dioxygenases,<sup>32</sup> successfully catalyze alkane C–H oxidations, which inspired the development of synthetic models to discover alkane oxidation catalysts. As Que Jr.’s insight discussed,<sup>33</sup> the critical fundamental principles have been revealed and underlain their efficacy as catalysts for aerobic oxidations. Based on such principles, great progress has been made to develop new ligands, synthetic catalysts, as well as catalytic processes for the alkane C–H bond oxidation.

Following their deep studies, Que, Jr. and co-workers reported a synthetic iron complex [Fe<sup>II</sup>(CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub>(<sup>Me</sup>PyTACN)], of which the crystal structure showed a distorted octahedral iron(II) center bearing a tetradentate ligand <sup>Me</sup>PyTACN and two

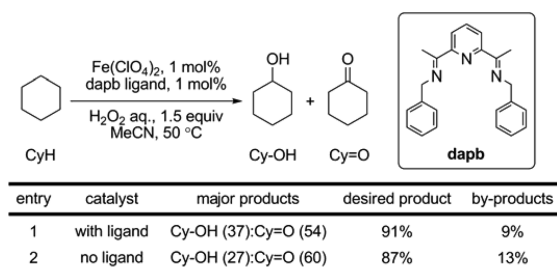
Scheme 4. Scenario How the Structure Played a Role in the Process of C–O Bond Formation



Scheme 5. Novel Family of Iron Complexes with TACN Backbone Ligands



Scheme 6. Efficient Iron-Catalyzed Oxidation of Cyclohexane C–H Bonds with/without dapb Ligand



triflate anions coordinated *cis* to each other.<sup>34</sup> This iron complex showed high catalytic reactivity for the oxidation of cyclohexane as well as other tertiary C–H's of *cis*-1,2-dimethylcyclohexane, adamantane, and 2,3-dimethylbutane. The H<sub>2</sub><sup>18</sup>O-labeling experiments indicated that the higher levels of H<sub>2</sub><sup>18</sup>O incorporation were obtained in the corresponding alcohols in the oxidation of alkanes with tertiary C–H bonds, such as adamantane (74%), *cis*-DMCH (79%), and 2,3-dimethylbutane (76%). Moreover, this result was found to be actually independent to the substrate concentration. Such results strongly suggested the HO–Fe<sup>V</sup>=O species as the only key oxidant toward alkane oxidation with iron complex [Fe<sup>II</sup>(CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub>]<sub>2</sub>(Me<sub>2</sub>PyTACN)]. Obviously, this oxidation process was significantly different from the formal case of Fe(TPA) (TPA = tris(2-pyridylmethyl)amine) and was described as an unusual rebound-like mechanism (Scheme 4). Notably, the *cis* configuration of the two hydroxy groups in this

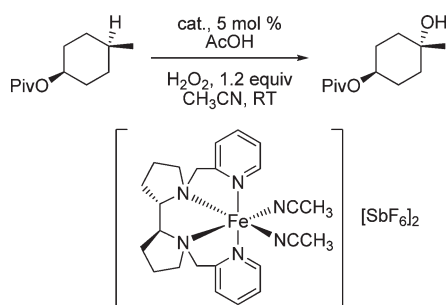
catalytic system is also different from the stereo requirement of the *trans* configuration in heme complexes and was a unique feature in these non-heme iron catalytic systems.

Later on, Costas expanded the tetradentate ligand Me<sub>2</sub>PyTACN to a “TACN” family, which owned a common methylpyridine derived triazacyclononane (TACN) backbone (Scheme 5).<sup>35</sup> This novel family of iron complexes exhibited unprecedented efficacy in the stereospecific oxidation of alkane C–H bonds and also dihydroxylation or epoxidation of alkenes. The catalytic selectivity in their reported oxidation systems can be tuned by modifying the structure of TACN ligands. The family of those complexes provides a versatile platform to mimic the iron-containing oxygenase-like system.

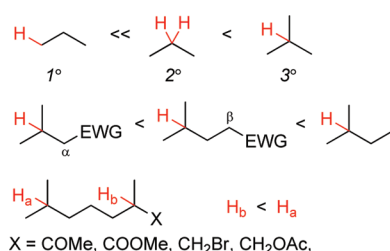
For the oxidation of cyclohexane (CyH), Reedijk reported a simpler and more efficient system by using catalytic amounts of commercial available iron salts (for example, Fe(ClO<sub>4</sub>)<sub>2</sub>) in acetonitrile under mild conditions, and H<sub>2</sub>O<sub>2</sub> as the oxidant.<sup>36</sup> The oxidation of CyH occurred rapidly and completely while the oxidation product was a mixture of cyclohexanol and cyclohexanone (Scheme 6). Interestingly, the counterions and the oxidative states of iron salts did not obviously affect the efficacy. Notably, when the simple tridentate N-ligand 2,6-bis[1-(benzylimino)ethyl]pyridine (dapb) was submitted, the selectivity of major products was to some extent enhanced, which promoted the applicable potential of this important transformation.

To approach the oxidation of general sp<sup>3</sup> C–H's, recently, White and co-worker made a significant improvement. In 2007, she and co-worker reported the iron catalyzed aliphatic C–H oxidation by using an iron (PDP) complex. In their report, a highly selective oxidation of nonactivated sp<sup>3</sup> C–H bonds via iron catalysis was well investigated (Scheme 7).<sup>37</sup> Iron (PDP) complex [PDP = 2-((S)-2-[(S)-1-(pyridin-2-ylmethyl)pyrrolidin-2-yl]pyrrolidin-1-yl)methyl]pyridine] was essential for this transformation and the higher rigid PDP ligand led to the increase of selectivity. This process was rather clean, since the oxidant was hydrogen peroxide, which was cheap, easily available, and frequently used in traditional iron-catalyzed Gif and Fenton chemistry.<sup>19,20</sup> In this transformation, the electronic feature rather than the steric effect of C–H bonds plays an important role, since electron rich tertiary C–H bonds showed a higher reactivity than either secondary or primary C–H bonds. An electron-withdrawing group on the α or β carbon of the C–H bond decreases the reactivity obviously. Furthermore, carbonyl, ester, acetate, and halogen functional groups tethered on substrates promote the selectivity. With such groups, the remote tertiary C–H bonds exhibit much better reactivities due to the

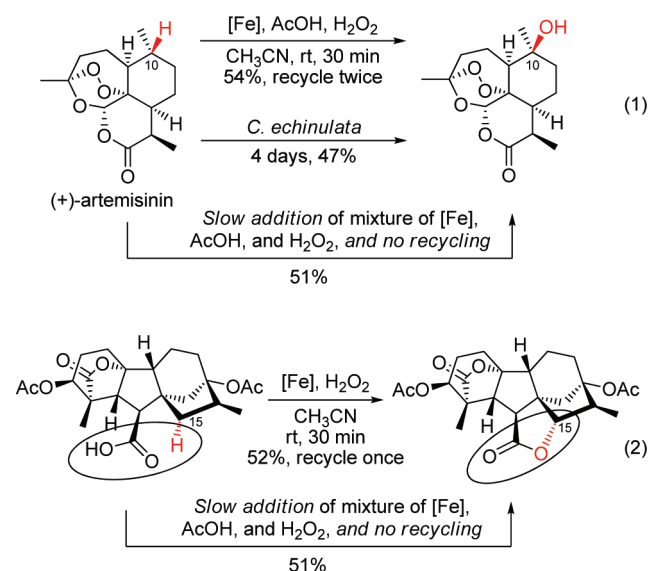
**Scheme 7. Iron-Catalyzed Oxidation of Unactivated  $\text{sp}^3$  C—H Bonds**



**Scheme 8. Reactivity of Different C—H Bonds**



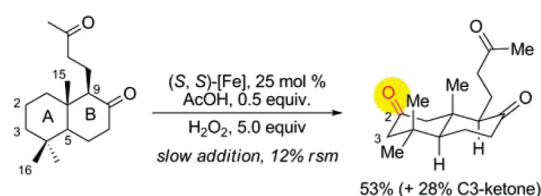
**Scheme 9. Synthetic Applications of Iron-Catalyzed Aliphatic C—H Oxidation**



decrease of electron density of close C—H's to them through their inductive effects (Scheme 8). Although no solid evidence and data supported the reaction pathway, the chemoselectivity and stereoselectivity outcomes of these iron-catalyzed C—H oxidations were consistent with a concerted mechanism mediated by an electrophilic oxidant.

Based on the selectivity principle above, the synthetic applications could be realized by selection of proper substrates. For

**Scheme 10. Combined Effects Lead to Predictable and Highly Selective Secondary C—H Bond Oxidations**

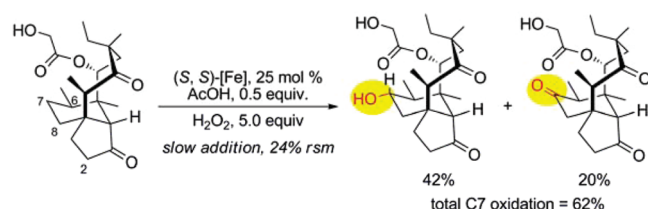


example, the  $\text{sp}^3$  C—H bond oxidation of the natural product (+)-artemisinin occurred at the most electron-rich and least sterically hindered site. Such an iron-catalyzed process afforded a higher yield, a higher volume throughput, and much shorter reaction time than enzymatic reaction (Scheme 9, eq 1). The carboxylate-directed hydroxylation and in situ lactonization of the tetrahydrogibberellic acid analogue via iron-catalyzed C—H oxidation generates the lactone product in 52% yield with once recycling of starting material (Scheme 9, eq 2). Furthermore, in the authors' following investigation, a slow addition protocol for the iron-catalyzed aliphatic C—H oxidation reaction was reported.<sup>38</sup> Under this protocol, the reaction could undergo higher conversions without decreasing site-selectivity or chemo-selectivity. In the example of two complex natural product derivatives in Scheme 5, hydroxylated products can be obtained in high isolated yields without the need for recycling recovered starting materials. This chemistry can be further successfully applied for diversifying natural products with high chemo- and regioselectivity, which exhibits promising potential in drug discovery.

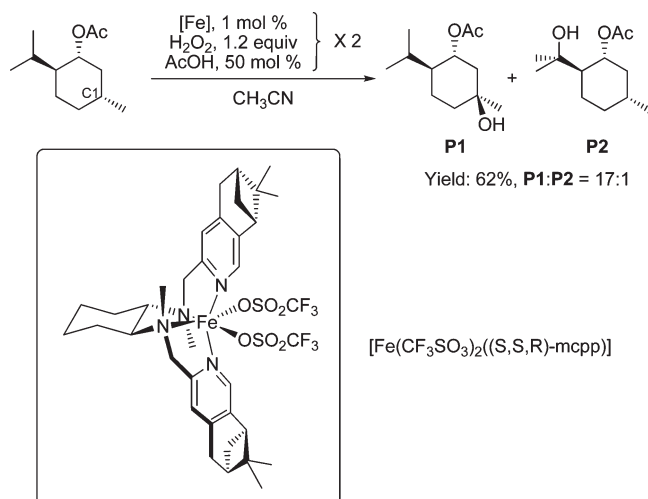
Encouraged by the significant results above, White and co-worker further developed selective secondary C—H bond oxidation and intensively investigated the combined effects in such iron-catalyzed secondary C—H oxidation.<sup>39</sup> Obviously, secondary C—H bonds have a lower electron density but a higher steric accessibility than tertiary C—H bonds. Furthermore, secondary C—H bonds are prevalent in ring systems. Therefore, the selective oxidation may provide a useful method for methylene functionalization. Electronic, steric, stereoelectronic, and functional group factors could individually promote the reactions with moderate selectivity in most cases. When a combination of these effects was taken into consideration, a higher level of chemo- and even diastereoselective oxidation would be achieved, especially in complex molecules.

Taking a dione as an example, the diterpenoid-derived dione contains 14 secondary C—H bonds and two tertiary C—H bonds. Based on the selectivity rules, two tertiary C—H bonds would be electronically and sterically deactivated. The side chain and the B ring should be electronically deactivated due to the electron-withdrawing carbonyl groups. The least bulky site on the A ring is C2, which should be the most activated site for oxidation. The results are consistent with the above prediction. The C2 oxidation product was obtained in 53% isolated yield, with another C3 oxidation product in 28% isolated yield and 12% recovered starting material (Scheme 10). Similarly, when another complex molecule, a pleuromutilin derivative, dihydropleuromutilone, was treated under standard conditions, a highly regio-, chemo-, and stereoselective C7 equatorial secondary C—H bond hydroxylation and further oxidation products were obtained (Scheme 11). This result was also consistent with the

**Scheme 11. Combined Effects Lead to Diastereoselective Methylene Oxidation**



**Scheme 12. Regiospecific Hydroxylation of (–)-Acetoxy-*p*-menthane**



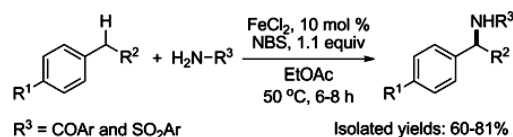
prediction based on the combined effects. This methodology would open a new strategy for selective C–H bond oxidation, which could be predictable by the fundamental electronic, steric, and other effects (such as directing effects by some certain functional groups) in organic chemistry.

In 2009, Ribas and Costas also reported a successful example of iron-catalyzed C–H oxidation.<sup>40</sup> The ligand was redesigned at the remote position of the pyridine ring with a more bulky hydrocarbon group, which helped to form a robust cavity for iron. This kind of iron complex obviously increased the selectivity and efficiency compared with the results in White's work. Take the oxidation of (–)-acetoxy-*p*-menthane for example, using iron complex [Fe(CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub>((S,S,R)-mcpp)] as catalyst: a regiospecific oxidation of tertiary C–H was realized in a good yield with only 1% loading of catalyst. Hydroxylation preferentially occurred in the more accessible (C1)–H bond to give the corresponding product (Scheme 12). Both electronic and steric factors played important roles in discrimination of different C–H bonds. This improvement greatly increased the potential and feasibility of the application of this iron-catalyzed methodology.

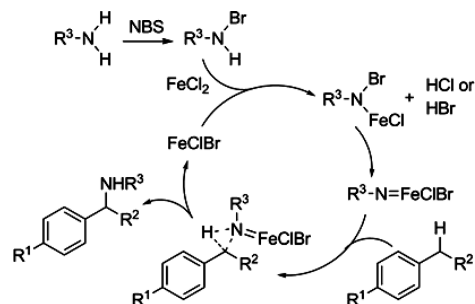
### 3. DIRECT C–N BOND FORMATION VIA OXIDATION OF A C–H BOND

Transition metal-mediated C–N bond formation via a C–H activation strategy is a significant process for construction of important nitrogen-containing organic compounds.<sup>41</sup> Compared

**Scheme 13. Iron-Catalyzed Amidation of Benzylic sp<sup>3</sup> C–H Bonds in the Presence of NBS**



**Scheme 14. Possible Mechanism for Iron-Catalyzed Amidation of Benzylic sp<sup>3</sup> C–H Bonds**

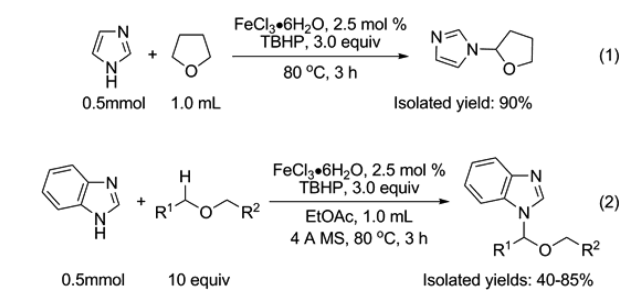


with widely developed and age-long C–O bond formation via C–H bond activation, the C–N bond formation from C–H's seems more difficult and was reported just in recent years. On the other hand, nitrene intermediates or nitrene derivatives were involved in most of the reported processes as the primary nitrogen source.<sup>42</sup> For example, PhI=NTs and its analogues have been widely applied in the C–H amidation reactions. Nevertheless, such hypervalent iodine reagents show their obvious disadvantages, and other developed alternative nitrene sources, such as chloramines-T,<sup>43</sup> bromamines-T,<sup>44</sup> and tosyl-oxycarbamates<sup>45</sup> have their own pitfalls. Therefore, the direct use of amines and amides as nitrogen sources is more challenging and attractive. Undoubtedly, the replacement of expensive late transition metals by economically competitive first-row transition metals is also an important aspect and will benefit synthetic applications.

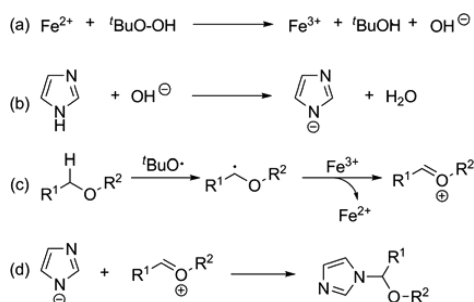
In 2008, Fu and co-workers reported the first example of iron-catalyzed amidation of C–H bonds.<sup>46</sup> In their studies, an efficient, inexpensive, and air-stable catalyst/oxidant system of amidation of benzylic sp<sup>3</sup> C–H bonds was developed by using carboxamides and sulfonamides as nitrogen sources. In this process, FeCl<sub>2</sub> is proven as the most efficient iron catalyst (Scheme 13). It is noteworthy that NBS (*N*-bromosuccinimide) is required to facilitate this transformation, which was considered as the efficient oxidant<sup>47</sup> and the free radical initiator.<sup>48</sup> In the investigation of the mechanism, the generation of *N*-bromocarboxamides and *N*-bromosulfonamides from NBS and amides is a key step to initiate the reaction. The intermediate iron–nitrene complex is formed and undergoes the following C–H bond activation step. The desired product was obtained after the removal of iron salts to fulfill the catalytic cycle in Scheme 14.

Besides the Fe–nitrene complex involved process, a new C–N formation process was demonstrated by Li in 2010.<sup>49</sup> In their report, iron-catalyzed oxidative C–N formation of azoles and ethers was achieved in good to excellent yields. The α-C–H bonds of oxygen in ethers were activated in the presence of iron

Scheme 15. Iron-Catalyzed Oxidative C–H Amination between Azole Derivatives and Various Ethers



Scheme 16. Possible Pathway of Iron-Catalyzed Oxidative C–N Bond Formation



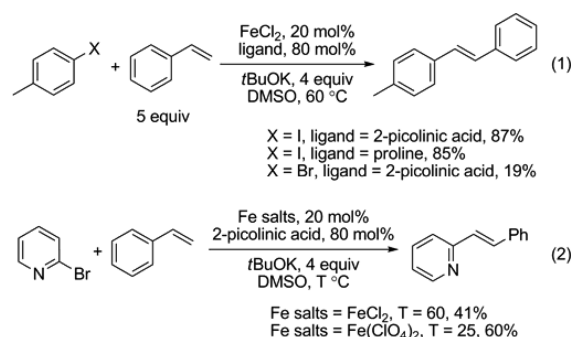
salts and radical initiators. The azoles reacted as good nitrogen-atom nucleophiles to fulfill such oxidative C–H bond amination reactions. In the presence of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  as the catalyst and TBHP (*tert*-butyl hydroperoxide) as the oxidant, imidazole and its derivatives went through this oxidative C–H amination smoothly with tetrahydrofuran in high yield (Scheme 15, eq 1). Under the optimized conditions, the investigation of reactions between benzimidazole and various ethers, using ethyl acetate as solvent, also exhibited good results (Scheme 15, eq 2).

A possible pathway of such oxidative C–N bond formation is considered in Scheme 16. Initially, TBHP decomposes into *tert*-butoxy radical and hydroxyl anion in the presence of the ferrous catalyst (step a). In the presence of in situ generated  $\text{OH}^-$ , deprotonation of an azole took place to afford the corresponding anion (step b). After a hydrogen abstraction of the C–H bond adjacent to an oxygen atom with the generation of oxonium ion by ferric oxidation (step c), the nucleophilic addition by azole anions to the oxonium ion produced the desired coupling product to fulfill the catalytic cycle (step d). Overall, the  $\text{Fe}^{2+} \rightarrow \text{Fe}^{3+}$  redox processes<sup>19a,c,d,20c</sup> play key roles in the present C–N bond formation. In fact, the author also mentioned that the exact catalytic cycle of this process is still unclear and requires further investigation.

#### 4. C–H BOND ARYLATION WITH ARYL HALIDES

The cross-coupling reaction now becomes one of the most useful tools to construct C–C bonds.<sup>50</sup> In the improvement of traditional cross-coupling reactions, the replacement of organometallic reagents by C–H bonds is an important direction to approach green and sustainable goals. In recent decades, much

Scheme 17. Iron-Catalyzed Mizoroki–Heck Reaction of Aryl Iodides/Bromides with Styrene

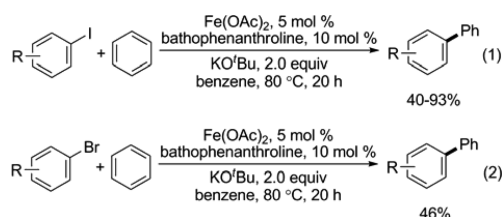
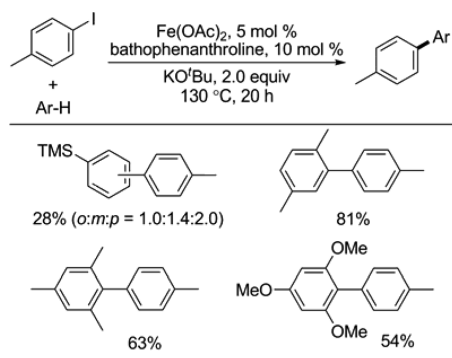


progress has been achieved successfully in the catalysis of  $\text{Pd}$ ,<sup>11,51</sup>  $\text{Ru}$ ,<sup>13a,15,51</sup>  $\text{Rh}$ ,<sup>13,15,51</sup> etc. The utilization of cheap first-row transition metals instead of noble metals is still challenging and elusive. Recent advances in this aspect were focused on  $\text{Cu}$ ,<sup>52</sup>  $\text{Ni}$ ,<sup>53</sup> and iron catalytic systems.

Palladium-catalyzed Mizoroki–Heck cross-coupling reaction of aryl halides with alkenes was first reported in 1970s<sup>54</sup> and now has become one of the most important methods for the construct of aryl-substituted olefins.<sup>55</sup> One of the coupling partners, aryl halide, has been developed from original aryl iodides to aryl bromides, chlorides, triflates, tosylates, mesylates, and diazonium salts.<sup>56</sup> Further investigation even developed aroyl chlorides,<sup>57</sup> esters,<sup>58</sup> and mixed anhydrides<sup>59</sup> as the coupling partners under decarbonylation conditions and arenesulfonyl chlorides as the coupling partners under desulfinylative conditions.<sup>60</sup> On the other hand, the substrates have been extended to the alkenyl derivatives.<sup>61</sup> Besides, another significant improvement is the replacement of  $\text{Pd}$  for relatively inexpensive and environment-friendly metals, such as  $\text{Ru}$ ,<sup>62</sup>  $\text{Ni}$ ,<sup>63</sup>  $\text{Co}$ ,<sup>63b,c,64</sup>  $\text{Cu}$ ,<sup>65</sup> and  $\text{Mn}$ . In 2008, Vogel reported a iron-catalyzed Mizoroki–Heck cross-coupling reaction of aryl iodides with styrenes.<sup>66</sup> In the presence of 20 mol %  $\text{FeCl}_2$ , 80 mol % picolinic acid and *t*-BuOK in DMSO (dimethyl sulfoxide), stereoselective cross-coupling reactions of (hetero)aryl iodides with styrenes produced the corresponding (*E*)-alkenes in 87% yield (Scheme 17, eq 1). As a ligand, proline gave a similar result as 2-picolinic acid (85%). Aryl bromides are also coupled with styrenes despite lower yields (Scheme 17, eqs 1 and 2). When using  $\text{Fe}(\text{ClO}_4)_2$  instead of  $\text{FeCl}_2$ , the yield of 2-bromopyridine was increased up to 60% after 24 h even at 25 °C (Scheme 17, eq 2). Unfortunately, other types of alkenes did not react well with low yields and regioselectivity.

Obviously, such iron-catalyzed Suzuki-type coupling is a proforma direct C–H transformation of alkenes. During this transformation, this iron-catalyzed reaction seemed to undergo a different process from conventional  $\text{Pd}$ -catalyzed Heck reactions. Supposedly, a radical pathway would be involved to facilitate this cross-coupling. More investigations are required to unveil such a catalytic transformation.

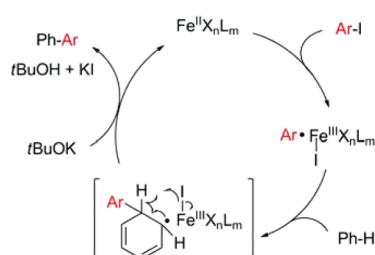
The C–H activation of common arenes and cross-coupling with aryl halides is another important aspect in transition metal catalyzed C–H transformation due to the significance of biaryl scaffolds. A recent advance exhibited a great prospect by using first-row transition metals to take the place of the precious late transition metals as catalysts. Copper-catalyzed cross-couplings of C–H bonds of various arenes with aryl halides were developed

**Scheme 18.** Iron-Catalyzed Direct Arylation of Benzene with Various Aryl and Heteroaryl Halides**Scheme 19.** Iron-Catalyzed Direct Arylation of Arenes with *p*-Tolyl Iodide

in recent years as important progress in this field.<sup>67,68</sup> Besides copper catalysis, a nickel-catalyzed process was also successfully introduced in cross-coupling of common arenes with aryl halides.<sup>69</sup> Those significant studies inspired chemists to search for other efficient transformations with other common first row transition metal catalysts. Very recently, Lei and Charette independently reported their successes on iron-catalyzed direct arylation of common arenes with aryl halides, which is a significant improvement in both iron chemistry and C–H activation.<sup>70</sup>

In Charette's observation, an iron-catalyzed direct arylation of unactivated arenes with aryl iodides was reported without the requirement of a stoichiometric amount of organometallic reagent. The directing group was also not necessary for this transformation.<sup>70a</sup> Under optimized conditions, a mixture of 4-iodotoluene (1 equiv), benzene (100 equiv), KO<sup>t</sup>Bu (2 equiv), Fe(OAc)<sub>2</sub> (5 mol %), and bathophenanthroline (10 mol %) at a relatively mild 80 °C provided the desired 4-methylbiphenyl in 86% yield. Various aryl iodides, including heteroaryl iodides, underwent this reaction in moderate to excellent yields (Scheme 18). However, aryl bromide gave the arylation product only in 46% yield. Different arenes were also applied to afford the corresponding biaryl products with aryl iodides in moderate to good yields (Scheme 19). Notably, the chemoselectivity is not good enough for the application unless the symmetric arenes were applied.

In their primary investigations of mechanism, the kinetic isotopic effect was 1.04, which suggested that the cleavage of the C–H bond was not involved in the rate-determining step. This cross-coupling was terminated in the presence of radical scavengers (TEMPO). Therefore, a possible radical pathway was

**Scheme 20.** Proposed Mechanism of Iron-Catalyzed Direct Arylation of Arenes with Aryl Iodides

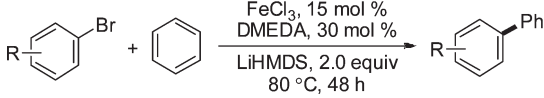
proposed. An initiating radical species was first formed through a reversible activation of Ar–X by a metal-assisted one-electron oxidation. Group transferring from ArX to Fe species to form an oxidized metallo-intermediate facilitated the oxidative addition. This metallo intermediate further attacked the arenes to form a  $\sigma$ -complex through the radical addition. Finally, the halide linked to Fe attracts the hydrogen from the  $\sigma$ -complex in a SET manner to produce the biaryls, with the reduction of the Fe center to facilitate the catalytic cycle. The requirement of base was considered to quench the in situ generated HI to keep the proper acidity of the reaction system (Scheme 20). The generation of *t*BuOH in the reaction mixture would support the function of the base. However, another role of *t*BuOK could not be ruled out at this stage. Such a radical process is completely different from well studied processes on C–H transformations, such as electrophilic substitution, oxidative addition, and  $\sigma$ -bond metathesis. Additionally, this radical process exhibited unexpectedly high efficiency and selectivity.

In Lei's report, FeCl<sub>3</sub> was more efficient than Fe(II) salts as catalyst and DMEDA was used as the best ligand. In the presence of LiHMDS as a base, less reactive aryl bromides showed good reactivity (Table 1). Similarly, aryl iodides also underwent this transformation smoothly and afforded the corresponding products when KO<sup>t</sup>Bu was used as a base (Scheme 21). Notably, unactivated aryl chlorides also reacted in spite of relatively low efficiency. Interestingly, electron-donating groups promoted the reactivity of aryl halides in both cases of aryl bromides and aryl iodides while steric hindrance obviously decreased the reactivity. Similarly as Charette's observation, the moderate yields and low selectivity were observed when the substituted arenes were applied as substrates.

At this stage, Lei and co-workers did not perform systematic experimental studies on the possible reaction pathway in their report. However, a similar radical process is considered, consistent with experimental observation and also the results in Charette's work. However, due to the use of Fe(III) salt instead of Fe(II) salts, the exact pathways might be completely different from the process proposed by Charette. Anyway, an application of the inexpensive, nontoxic, commercially available, and environmentally benign iron catalysts in cross-coupling attracts more attention, which may have broader applications in organic synthesis in the near future.

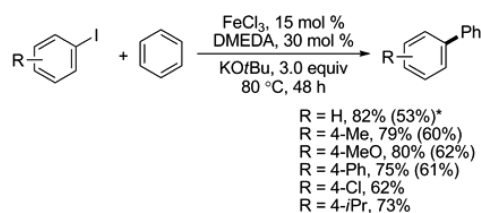
## 5. DIRECT C–H ARYLATION WITH ORGANOMETALLIC REAGENTS

Compared to the direct arylation of aryl C–H bonds with aryl halides, C–C bond formation via iron-catalyzed direct arylation of aryl C–H bonds with organometallic reagents was developed

**Table 1. Iron-Catalysis of Different Aryl Bromide Couplings with Benzene<sup>a</sup>**


entry	Ar	yield (%) <sup>b</sup>	entry	Ar	yield (%) <sup>b</sup>
1	Ph	77	7	4- <i>t</i> BuC <sub>6</sub> H <sub>5</sub>	72
2	4-MeOC <sub>6</sub> H <sub>5</sub>	81	8	4-Ph <sub>2</sub> NC <sub>6</sub> H <sub>5</sub>	72
3	2-MeOC <sub>6</sub> H <sub>5</sub>	37	9	4-PhC <sub>6</sub> H <sub>5</sub>	63
4	4-MeC <sub>6</sub> H <sub>5</sub>	73	10	4-CNC <sub>6</sub> H <sub>5</sub>	51
5	3-MeC <sub>6</sub> H <sub>5</sub>	73	11	4-FC <sub>6</sub> H <sub>5</sub>	45
6	2-MeC <sub>6</sub> H <sub>5</sub>	45	12	2-naphthyl	70

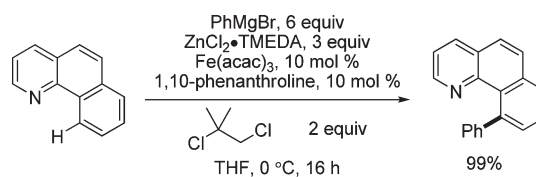
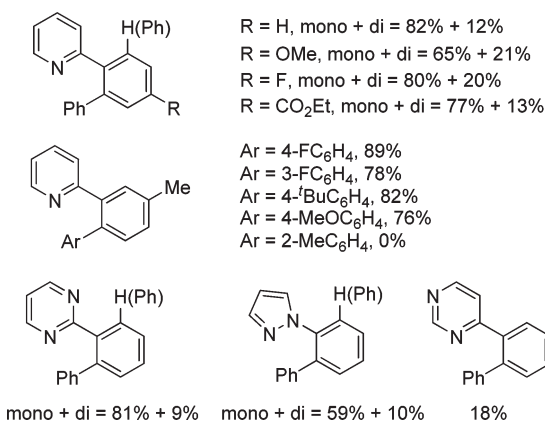
<sup>a</sup> All the reactions were carried out on the scale of 0.5 mmol of aryl bromides in benzene (4.0 mL, 45 mmol). <sup>b</sup> Isolated yields.

**Scheme 21. Iron-Catalysis of Different Aryl Iodides Coupling with Benzene<sup>a</sup>**

<sup>a</sup> In parentheses, the reactions were carried out using LiHMDS.

a little earlier. In 2008, Nakamura and co-workers developed the first iron-catalyzed direct arylation of aryl C–H bonds with in situ generated organozinc reagents from aryl Grignard reagents and ZnCl<sub>2</sub> in the presence of a proper ligand.<sup>71</sup> Obviously, the oxidant was demanded to facilitate such an oxidative coupling. After the optimization, 1,2-dichloroisobutane exhibited a good reactivity to promote this transformation. The proper ligand was also essential for this coupling. Although different bidentate or tridentate nitrogen-containing ligands showed some reactivities, 1,10-phenanthroline was found to be the most effective one after the systematic investigations (Scheme 22).

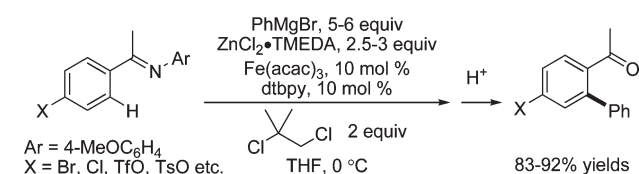
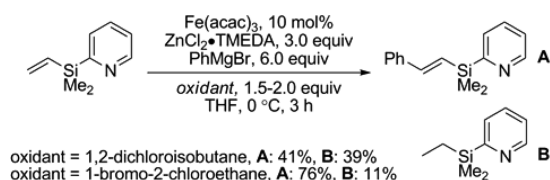
Similar to the general strategy to control the regioselectivity of direct C–H transformations via late transition metal catalysis, the regioselectivity of this study was also successfully controlled by the N-contained anchoring group. Starting from  $\alpha$ -benzoquinoline, the arylation was exclusively observed at the C-10 position. Directed by the pyridinyl group, only *ortho* arylation was observed. This arylation was very sensitive to the steric hindrance, and the presence of a 3-methyl group on the phenyl ring of 2-phenylpyridine allowed the phenylation to take place exclusively on the less hindered position opposite to the methyl group. Notably, substrates bearing either an electron-donating or an electron-withdrawing substituent on the 4-position of the phenyl ring reacted smoothly to give the corresponding phenylated products in good yields, in spite of being accompanied by diarylated products as a mixture. Similarly, various arylzinc reagents were suitable for this transformation, indicating the insensitivity to the electronic effect in both substrates and

**Scheme 22. Phenylation of  $\alpha$ -Benzoquinoline with Phenylzinc Reagent****Scheme 23. Iron-Catalyzed Arylation of 2-Arylpyridine Derivatives with Arylzinc Reagents**

arylzinc reagents. However, the extremely low coupling rate with 2-tolylzinc reagent suggested the critical role of the steric effect. Moreover, other nitrogen-containing heterocycles, for example, 2-phenylpyrimidine and 1-phenyl-1*H*-pyrazole also exhibited good reactivities (Scheme 23). Although the reaction rate was somewhat slower, this observation suggested the promising application of this method in organic synthesis.

Later on, the same research group extended their research to general aromatic imines. In this study, they found dtbpy (4,4'-di-*tert*-butyl-2,2'-bipyridine) showed the best reactivity as a ligand to take the place of 1,10-phenanthroline. This method resulted in direct functionalization of the *ortho* C–H bond of aromatic ketimines with arylzinc reagents, providing a convenient method for the construction of *ortho*-substituted aromatic ketones and ketimines.<sup>72</sup> Applicably, this transformation showed a broad substrate scope. Most importantly, a unique feature of this reaction was that such a direct arylation still occurred preferentially in the presence of various leaving groups, such as Cl, Br, OTs, as well as OTf, which offered a great chance for the orthogonal functionalization through traditional cross-coupling (Scheme 24). Later on, their investigations significantly improved their transformations by using dioxygen as an oxidant instead of expensive organodichlorides.<sup>73</sup> By slowly introducing dioxygen into the reaction, the desired oxidative cross-coupling took place smoothly, indicating its potential of synthetic application. The mechanism of this reaction seems quite complicated and may be completely different from traditional pathways. Anyway, further studies of the mechanism are still required and attractive.

Other than the oxidative cross-coupling to afford biaryl compounds, an "oxidative Heck-type" reaction was reported.<sup>74</sup>

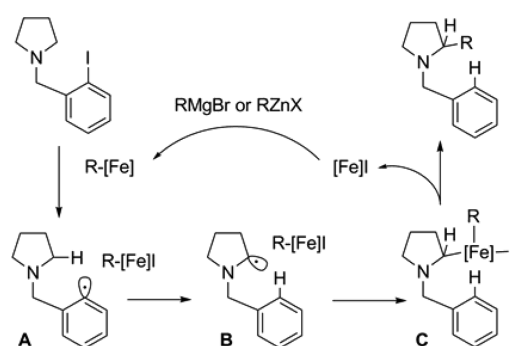
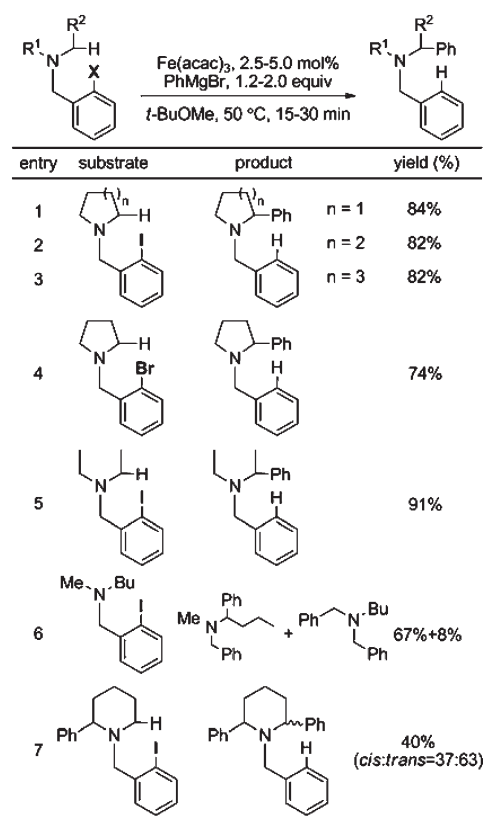
**Scheme 24. Iron-Catalyzed Coupling of (Pseudo)halogen-Bearing Aryl Imines and a Diphenylzinc Reagent****Scheme 25. Iron-Catalyzed Directed Oxidative Arylation of Olefins with Organozinc Reagents**

In the presence of Fe catalyst, the oxidative coupling took place smoothly between aryl Grignard reagents and 2-pyridinyl vinyl-silenes. Interestingly, the major difference in this system from previous work on pyridine- and imine-directed C–H activation was the oxidant. In these studies, 1-bromo-2-chloroethane was found to be more efficient than 1,2-dichlorobutane, which efficiently suppressed the formation of the reduced byproduct (Scheme 25).

The success in iron-catalyzed C(sp<sup>2</sup>)–H activation encouraged the further investigation of an iron-catalyzed C(sp<sup>3</sup>)–H bond activation. Nakamura first reported a successful iron-catalyzed intermolecular coupling of sp<sup>3</sup> C–H adjacent to the N atom bearing an *N*-(2-iodophenyl)methyl group with organozinc reagents or Grignard reagents.<sup>75</sup> The *N*-IBn (*N*-(2-iodobenzyl)) group tethered on the amine would serve as an internal trigger for the cleavage of the C–H bond next to the nitrogen group. Supposedly, the reaction was initiated by the iron-mediated deiodination, and an aryl radical intermediate **A** was generated (Scheme 26). The conversion of intermediate **A** into **B** through 1,5-hydrogen transfer occurred,<sup>76</sup> followed by formation of an organoiron intermediate **C**. Reductive elimination on the iron center resulted in formation of C(sp<sup>3</sup>)–C(sp<sup>2</sup>) to produce the final desired product. Similar to previous work, the exact mechanism is still unknown and the studies are required.

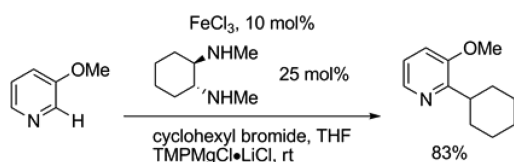
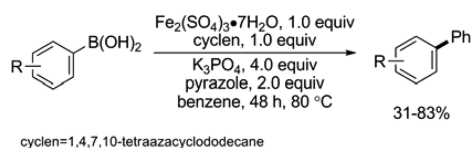
With the developed condition, various aliphatic amines, including five-, six-, and seven-membered cyclic amines (Scheme 27, entries 1–3) as well as acyclic aliphatic amines (entries 5, 6), underwent this transformation smoothly. The bromo analogue could also undergo this reaction while in a lower yield (entry 4). The phenylation of the asymmetric *N*-methyl-*N*-butylamine took place preferentially at the more substituted chain (entry 6), which supported the assumption of the radical intermediates. 2-Phenylpiperidine gave the phenylation product only in 40% yield at the 6-position to give 2,6-diphenylpiperidine with modest diastereoselectivity (entry 7).

Very recently, Daugulis also reported an iron-catalyzed deprotonative alkylation of arene C–H bonds by alkyl iodides and bromides.<sup>77</sup> Notably, the substrates were furans, thiophenes, pyridine derivatives, and some arenes bearing electron-withdrawing groups, and the C–H activation step was indeed a

**Scheme 26. Pathway of Iron-Catalyzed C(sp<sup>3</sup>)–H Bond Arylation****Scheme 27. Iron-Catalyzed  $\alpha$ -Functionalization of Aliphatic Amines with Grignard Reagents**

deprotonation by base (Grignard reagents here). Therefore, this reaction was more like an iron-catalyzed cross-coupling of aryl metallic reagents and organohalides. An example was described in Scheme 28.

Other than the cross-coupling with organozinc reagents, Yu first reported a beautiful example of iron-mediated direct arylation of unactivated arenes with arylboronic acids.<sup>78</sup> Under the optimized conditions, various boronic acids underwent this transformation in moderate to good yields (Scheme 29). The use of arylboronic acids makes such a transformation feature good functional group compatibility and opens the possibility to

**Scheme 28. Iron-Catalyzed Deprotonative Alkylation of Arene C–H Bonds****Scheme 29. Iron-Mediated Arylation of Benzene with Arylboronic Acid**

carry out C–C coupling of polyfunctional systems. Similarly, the mechanism of this process was still undeveloped.

Iron salts were used in a stoichiometric amount in the process above. A catalytic version was also achieved in the author's following investigation. An iron-catalyzed direct Suzuki–Miyaura reaction between *N*-heterocyclic arenes and aryl boronic acids was reported.<sup>79</sup> Macrocyclic polyamines (MCPA) were introduced and well studied in this iron-catalyzed process. Taking pyrroles as substrates, the best result was obtained in the reaction using  $\text{FeC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$  as catalyst and pyridine-containing ligand **L** as the MCPA ligand, and the amounts of Fe–MCPA complex could be decreased to 20 mol % when air was present as terminal oxidant. Under the optimized conditions, various aryl boronic acids and pyrroles could undergo this transformation smoothly (Scheme 30). It is noteworthy that the arylation occurred exclusively at the C2 position of pyrroles.

## 6. C–C BOND FORMATION VIA CROSS-DEHYDROGENATIVE COUPLING (CDC)

The construction of C–C bonds is one of the most important tasks in organic synthesis. Among various methods to construct C–C bonds, the direct coupling of two C–H bonds is the most efficient, environmentally benign, and straightforward method, by avoiding the use of either organo halides/pseudohalides or organometallic reagents. Thus, the transition metal catalyzed methodologies starting from two different C–H bonds have attracted much attention.<sup>80</sup> Other than late and noble transition metal catalysts, Li and co-workers made a significant contribution to develop a series of synthetic methodologies to form the carbon–carbon bonds directly from two different carbon–hydrogen bonds under oxidative conditions via first row transition metal catalysis, which was named as the cross-dehydrogenative-coupling (CDC).<sup>81</sup> In their initiating work, cheap and simple copper salts were the most popular catalyst and a radical process was proposed. Later on, after Li's report of the first example of iron-catalyzed CDC reactions in 2007,<sup>82</sup> many groups followed and made significant contributions in this field. In this part we review the iron-catalyzed CDC reaction, classified according to different hybridizations of both the carbon reaction centers.

### 6.1. CDC of Two $\text{sp}^3$ C–H Bonds

In Li's earliest investigations, diphenylmethane was chosen as the standard substrate, due to the double activation at the benzylic position, to realize the CDC reaction with the active 1,2-dicarbonyl compounds with Cu or Co salts as catalysts. Later on, benzylic C–H bond activation in CDC was first realized by iron catalysis. Interestingly, iron catalysis was found to be even more effective than the previously used copper or cobalt catalysts. Among various iron salts,  $\text{FeCl}_2$  exhibited the best efficacy, cleanly providing the corresponding CDC products in moderate to excellent yields (Scheme 31).<sup>82</sup> The use of di(*tert*-butyl) peroxide (DTBP) to take the place of TBHP as an oxidant further increased the yield. Notably, this is the first example of an iron-catalyzed CDC reaction, which has initiated the application of iron catalysis in this field.

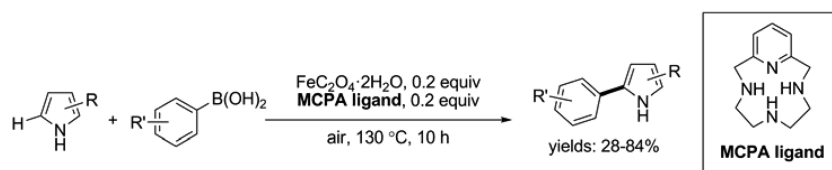
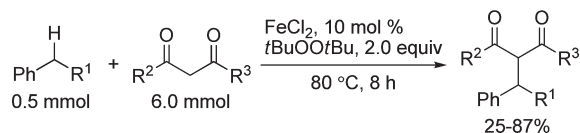
Similarly, this iron-catalyzed CDC reaction might undergo a possible single-electron transfer pathway as shown in Scheme 32. Through the homolysis of DTBP in the presence of  $\text{Fe(II)}$ , both *tert*-butoxyl radical and  $\text{Fe(III)}$  were formed. After the different proton abstractions, two key intermediates,  $\text{Fe(III)}$  enolate and benzyl radical, were generated. After the C–C construction through the electrophilic radical attack, the desired cross-coupling products were obtained, accompanied by the regeneration of  $\text{Fe(II)}$  species to facilitate the catalytic cycle.

Another type of  $\text{sp}^3$  C–H bonds which can be successful applied into the CDC reaction is those adjacent to nitrogens of amines or to oxygens of ethers. The  $\alpha\text{-sp}^3$  C–H bond of nitrogens in amines or oxygens in ethers can be readily activated to generate iminium or oxonium ions via single electron-transfer (SET) processes by transition metals<sup>81,83b</sup> or by other ways.<sup>83b</sup> The intermediate iminium or oxonium can undergo a further reaction with a carbon nucleophile to form a new C–C bond (Scheme 33). Traditionally, transition metals play a critical role as initiators to facilitate this transformation in the presence of a stoichiometric amount of hydrogen acceptors, such as peroxides and benzoquinones. Li and co-workers have made significant contributions in the copper-catalyzed CDC reactions of  $\alpha\text{-C-H}$  bonds of nitrogens in amines and  $\alpha\text{-C-H}$  bonds of oxygens in ethers.<sup>84,85</sup> Although these reactions still had the limitation of substrates and relative low efficiency, the mild and simple condition and great prospect of applications attracted more and more attention. Significant progress has been made recently, especially on the iron-catalyzed processes.

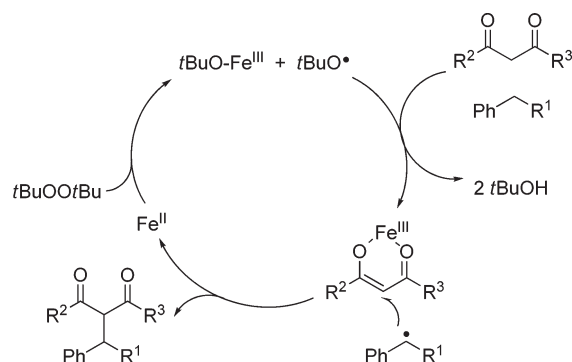
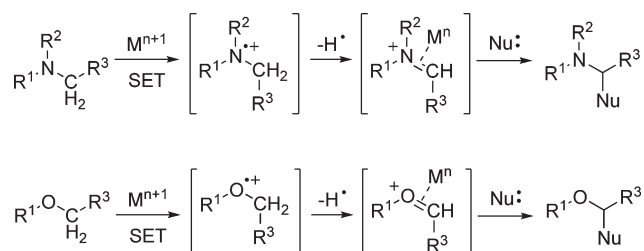
Inspired by the success of iron-catalyzed CDC with biphenylmethane derivatives, Li and co-workers reported an iron-catalyzed C–C bond formation by direct functionalization of  $\alpha\text{-C-H}$  bonds of oxygen in ethers with 1,3-dicarbonyl compounds.<sup>86</sup> In these studies,  $\text{Fe(OAc)}_2$ ,  $\text{FeCl}_2$ ,  $\text{FeBr}_2$ , and  $\text{Fe}_2(\text{CO})_9$  were found to be efficient catalysts to approach the CDC of THF and benzoylacetates. Under the optimized conditions, both acyclic and cyclic ether derivatives reacted smoothly with different 1,3-dicarbonyl substrates to give the corresponding products in moderate to excellent yields. Notably, sulfide and amine groups were also suitable substrates in this unprecedented transformation. For example, either tetrahydrothiophene or *N,N*-dimethylaniline could be used, and the desired CDC products were afforded in good to excellent yields (Scheme 34). Undoubtedly, these studies highly expanded the substrate scope for this desired CDC cross-coupling, which made such a transformation much more attractive for potential applications.

Subsequently, Li and co-workers extended their work with the use of *N,N*-dimethylaniline as a substrate and reported an

Scheme 30. Iron-Catalyzed Arylation of Substituted Pyrroles with Phenylboronic Acids

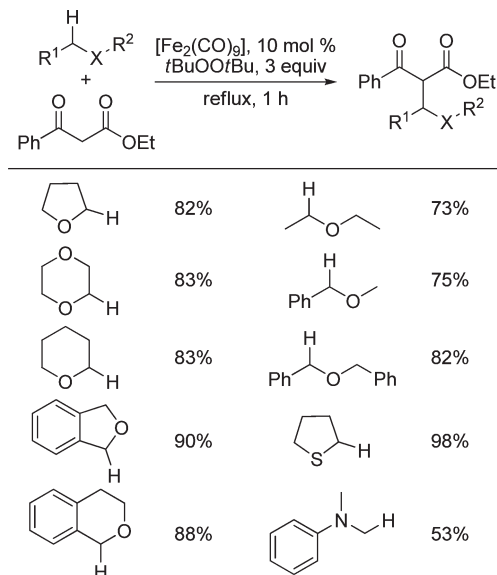
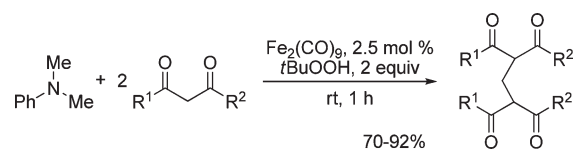
Scheme 31.  $\text{FeCl}_2$ -Catalyzed Selective CDC of Benzylic C–H Bonds

Scheme 32. Tentative Mechanism for the Iron-Catalyzed CDC Reaction

Scheme 33. General Processes in the CDC Reactions of the  $\alpha$ -C–H Bond of Nitrogens in Amines and the  $\alpha$ -C–H Bond of Oxygens in Ethers

unprecedented dialkylation of the methylene group from the methyl moiety of *N,N*-dimethylaniline.<sup>87</sup> In this study, 2 equiv of 1,3-dicarbonyl compounds were consumed and methylene-bridged bis-1,3-dicarbonyl compounds were obtained in high efficiency. Among all the iron catalysts,  $\text{Fe}_2(\text{CO})_9$  exhibited an excellent catalytic ability (Scheme 35). Several different possible pathways were proposed as described in Scheme 36. In Li's proposal, two substrates underwent an iron-catalyzed CDC

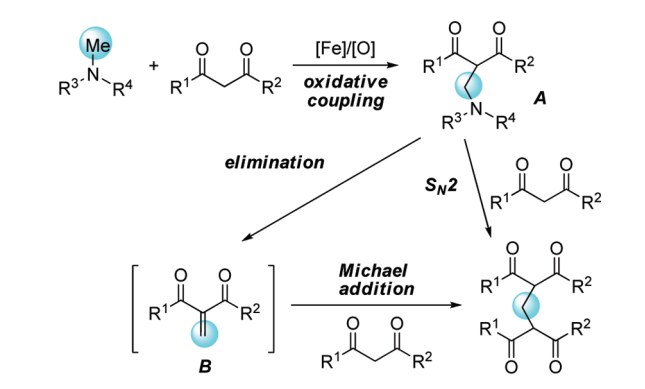
Scheme 34. Iron-Catalyzed C–C Bond Formation by Direct Functionalization of C–H Bonds Adjacent to Heteroatoms

Scheme 35. Iron-Catalyzed Selective CDC Reactions of *N*-Methyl Amines with 1,3-Dicarbonyl Compounds

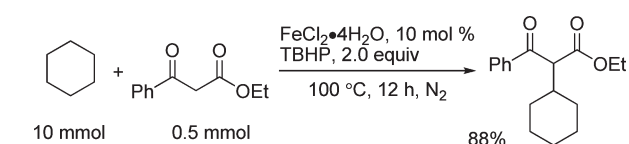
reaction to form intermediate **A** based on the previous studies. This intermediate **A** might undergo direct  $\text{S}_{\text{N}}2$  substitution by the second molecule of 1,3-dicarbonyl compound to afford the final product, with *N*-methylaniline as a leaving group. The other feasible pathway may be initiated by a Cope elimination from intermediate **A** to create a Michael acceptor **B**, followed by a subsequent Michael addition with a second molecule of 1,3-dicarbonyl compound to form the final product. On the other hand, the desired product was also afforded from 1,3-dicarbonyl compounds and formaldehyde, which was supported by the independent experiment (Scheme 36). Thus, the pathway through in situ generated formaldehyde via iron-catalyzed oxidation of *N*-dimethylaniline cannot be rooted out.

Among direct C–H transformations, general alkyl  $\text{sp}^3$  C–H faces the highest challenge due to its intrinsic inactivating

**Scheme 36.** Possible Pathways for the Iron-Catalyzed Selective CDC Reactions of *N*-Methyl Amines with 1,3-Dicarbonyl Compounds



**Scheme 37.** Alkane Alkylation via a  $\text{FeCl}_2$ -Catalyzed CDC Reaction

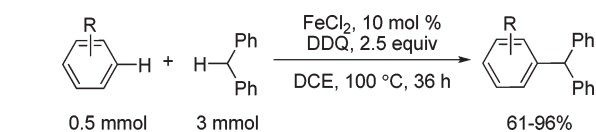


features. Inspired by Fenton chemistry and Gif processes as well as the previous successful studies, Li and co-workers reported a beautiful example to approach the ideal CDC transformation with alkanes via iron catalysis. The condition screening indicated that  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  was the best catalyst and *tert*-butyl peroxide was the most efficient oxidant. The cycloalkane was preferably submitted to the catalytic condition by avoiding the difficulty of the regio- and chemoselectivity. The desired CDC products with 1,3-dicarbonyl compounds were obtained in good efficiency although the reaction condition was relatively harsh (at 100 °C for 12 h under  $\text{N}_2$ ) (Scheme 37). Until now, this has been the only successful example of application of unactivated alkane as substrates in such a class of transformations.<sup>88</sup> The reaction was also proposed to go through a similar radical process in the iron-catalyzed CDC reaction of relatively active C–H bonds. All these studies successful turned the Fenton and Gif oxidation process of alkanes into a C–C bond formation reaction by intercepting the intermediate.

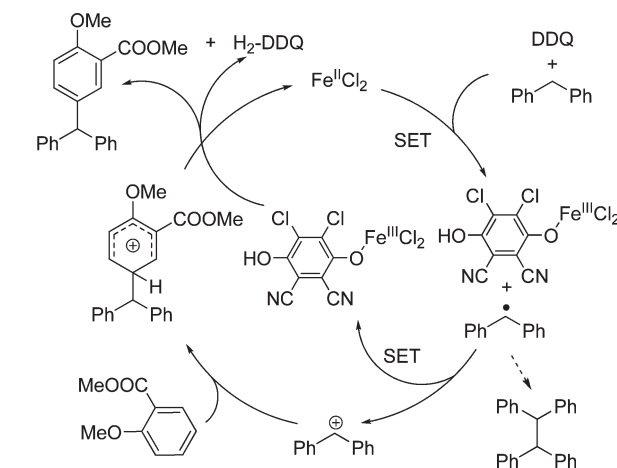
## 6.2. CDC between $\text{sp}^2$ and $\text{sp}^3$ C–H Bonds

Actually, the “CDC” reactions to form an  $\text{sp}^3$  and  $\text{sp}^2$  C–C bond were early described by Minisci.<sup>89</sup> The hypothesized pathway involves the radical generation of an  $\text{sp}^3$  centered carbon, which adds to the olefin or to protonated heterocycles. With the interpretation of the intermediates in the CDC between dibenzylmethane and 1,3-bicarbonyl compounds in Li’s CDC reaction system above, other nucleophiles were further considered to quench the intermediate based on the iron-catalyzed SET process from diphenylmethane derivatives. In 2009, Shi and co-workers reported an unprecedented iron-catalyzed cross-dehydrogenative arylation (CDA) of benzylic C–H bonds with electron-rich arenes.<sup>90</sup> DDQ was observed as the efficient oxidant to facilitate this transformation. This oxidant also

**Scheme 38.** Iron-Catalyzed Cross-Dehydrogenative Arylation of Aryl C–H Bonds with Benzylic C–H Bonds



**Scheme 39.** Proposed Mechanism for Cross-Dehydrogenative Arylation



exhibited its priority for safety considerations other than peroxides. Generally, diarylmethane was used as a solvent to approach the high efficacy. However, the use of dichloroethane (DCE) as a solvent highly reduced the amount of diphenylmethane and also resulted in an excellent yield of the desired product under the optimized conditions (Scheme 38). Various electron-rich arenes and different diarylmethanes were suitable substrates with excellent regioselectivity, controlled by the electronic properties of arenes. With the more electron rich arenes, double CDAs were also observed at high efficiency.

Mechanistically, this reaction was initiated by the iron-assisted SET oxidation to generate the benzyl radical, which could be further oxidized to the benzyl cation. A subsequent Friedel–Crafts-type process, followed by abstraction of the proton by the reduced hydroquinone, afforded the coupling product and regenerated the catalyst (Scheme 39). Recently, intra- and intermolecular direct arylation of alkyl C–H have been investigated by using other transition metal catalysts,<sup>91</sup> but such an iron-catalyzed transformation exhibited its uniqueness and advantages due to the feature of iron elements and the use of environmentally benign oxidants. The mildness and simplicity of this transformation may provide a practical and competitive perspective in organic synthesis in the near future.

In Shi’s subsequent studies, electron rich alkene was further considered as a nucleophile to quench the generated radical or cationic intermediates via an iron-catalyzed SET process. In their early studies, they found the styrene could be applied to construct C–C bonds with diphenylmethane by CDC in the Heck-type reaction. However, only styrene was observed as an efficient substrate. Other styrene derivatives with either electron-rich or electron-deficient groups on the phenyl ring failed in this

**Table 2.** C–C Bond Formation via Iron-Catalyzed Benzylic C–H Activation<sup>a</sup>

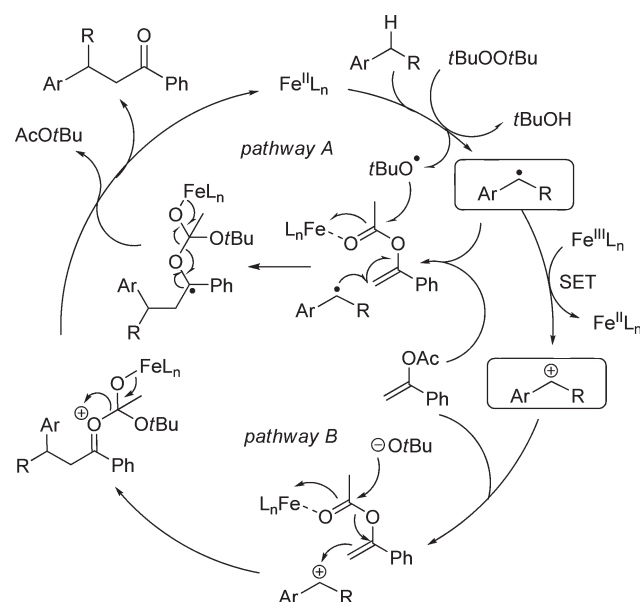
entry	Ar	R	yield (%)
1	Ph	Ph	74
2	4-FC <sub>6</sub> H <sub>5</sub>	4-FC <sub>6</sub> H <sub>5</sub>	62
3	4-FC <sub>6</sub> H <sub>5</sub>	Ph	73
4	4-ClC <sub>6</sub> H <sub>5</sub>	Ph	63
5	4-PhC <sub>6</sub> H <sub>5</sub>	Ph	77
6	4-MeOC <sub>6</sub> H <sub>5</sub>	Ph	45
7	2-MeOC <sub>6</sub> H <sub>5</sub>	Ph	13
8	2-naphthyl	Ph	69

<sup>a</sup> The reaction was carried out in 4.0 mmol of benzylic compounds and 0.5 mmol of acetates in the presence of 0.6 mmol of DTBP and 0.05 mmol of FeCl<sub>2</sub> under N<sub>2</sub> at 100 °C for 24 h, and isolated yields were obtained.

transformation. This is by now the only case to facilitate C–C bond formation through this process via Fe catalysis. Later on, 1-aryl vinyl acetate was further applied to take the place of styrene.<sup>92</sup> The reaction ran very smoothly to get the cross-coupling products in good to excellent yields in the presence of FeCl<sub>2</sub> and *t*BuOO*t*Bu. Different from styrene, these transformations produced keto products with vinyl acetates in a pseudo sp<sup>3</sup>C–sp<sup>3</sup>C coupling manner. Under the developed conditions, various vinyl acetates and diarylmethane were tested. Other than a highly electron-deficient group, general substituents, such as methoxyl, alkyl, aryl, and halides, did not obviously affect the efficiency. In contrast, both electron-rich and electron-deficient substituents on the phenyl ring of diarylmethanes were compatible. Notably, simple toluene also fits for this transformation with a moderate yield (Table 2).

Similarly, this transformation was highly preferred to the single electron transfer (SET) pathway.<sup>37,82,88</sup> Two possible catalytic cycles were proposed as Scheme 40. In pathway A, a radical intermediate and a *t*BuO radical were generated from the initiating step with DTBP in the presence of Fe catalyst, and they underwent subsequent electrophilic addition to vinyl acetate to form the Fe-coordinated radical intermediate. After the β-scission, the desired product was produced, accompanied by the regeneration of Fe(II) catalyst as well as AcO*t*Bu as a byproduct. The observation of *tert*-butyl ether and dimerization of diphenylmethane supported the production of the benzyl radical species. The other possibility was the cationic pathway (Scheme 40, pathway B). In this assumption, the radical intermediate might be further oxidized to a benzyl cation, which was quenched by vinyl acetates to produce the desired products. An intermolecular isotopic competitive study (*K*<sub>H/D</sub> = 2.4) indicated that the proton abstraction process may be involved in the rate determining step in either pathway. Notably, the observed electronic feature of diarylmethane substrates does not meet this hypothesis of path B from the original report.

The same idea could also be extended to the sp<sup>3</sup> C–H adjacent to heteroatoms. In 2009, Li and co-workers reported the iron-catalyzed CDC reaction of the C–H bond adjacent to

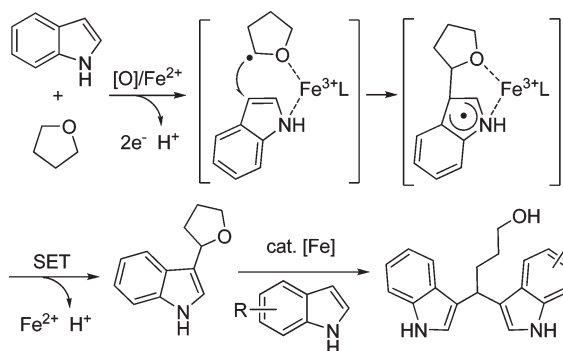
**Scheme 40.** Proposed Mechanism of C–C Formation via Iron-Catalyzed Benzylic C–H Activation

the oxygen atom of ethers with electron-rich arenes as the carbon nucleophile. Followed by the Friedel–Crafts transformation with the in situ generated ether adducts, 1,1-biaryl products were produced in good to excellent efficiency. To clarify the mechanism of this transformation, two different indoles were introduced at different steps. The result indicated that the first indolation step was less influenced by the electronic properties of indoles, but the second indolation step highly depended on the electron density of indoles, which meets the agreement of the Friedel–Crafts aromatic alkylation.<sup>93</sup> Therefore, the first step was likely a radical process, which was similar to other iron-catalyzed CDC processes (Scheme 41). Notably, this method could be applied in the one-pot synthesis of symmetric and asymmetric 1,1-bis(indolyl)methane derivatives. For example, when an electron-deficient indole was used in the first step and then electron-rich indoles were used in the second step, asymmetric 1,1-bis(indolyl)methane derivatives were obtained exclusively in high yields (Scheme 42).

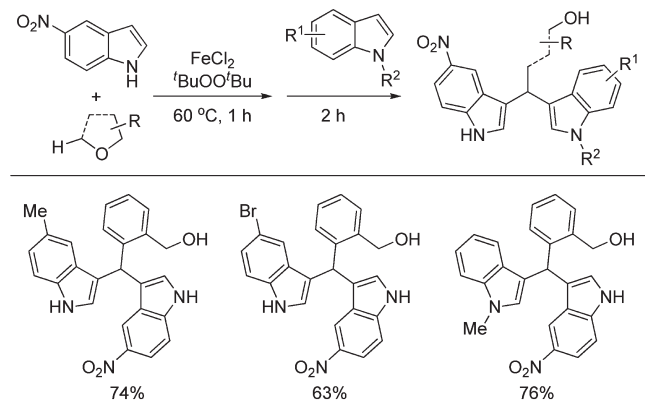
Very recently, Li and co-workers made a possible breakthrough in the construction of polysubstituted benzofurans via iron-catalyzed CDC reaction and the subsequent annulation by using phenols and β-keto esters as substrates.<sup>94</sup> In this unprecedented process, various iron salts did not affect the efficiency very much. Notably, the water in iron catalysts promoted the reaction greatly (Scheme 43). For example, the reaction was carried out in the presence of FeCl<sub>3</sub>·6H<sub>2</sub>O and showed high efficacy. The addition of 4A-MS to quench the water dramatically terminated this transformation. Similarly, other Brønsted acids, such as methanol, ethanol, acetic acid, benzoic acid, and *tert*-butanol, could also be proton sources to take the place of H<sub>2</sub>O to promote this transformation.

The catalytic cycle was hypothesized as Scheme 44. An intermediate Fe<sup>n+</sup>-chelated species A was formed in situ, followed by reductive elimination to produce the adduct B. After the tautomerization of B to the corresponding phenol C, the benzofuran is formed by intramolecular condensation in the

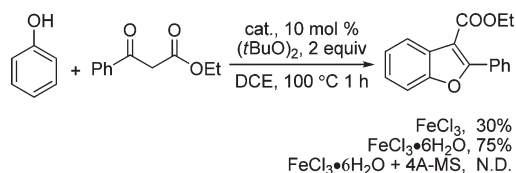
**Scheme 41.** Tentative Mechanism of Tandem Iron-Catalyzed C–H Bond Oxidative Coupling and C–O Bond Cleavage



**Scheme 42.** Tandem Iron-Catalyzed C–H Bond Oxidative Coupling and C–O Bond Cleavage



**Scheme 43.** Iron-Catalyzed Tandem Oxidative Coupling and Annulation To Construct Polysubstituted Benzofurans

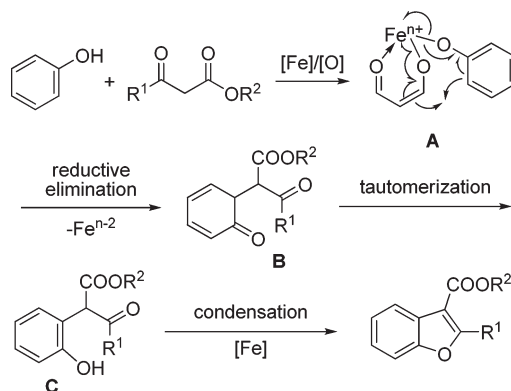


presence of iron catalyst. This proposal was partially supported by the successful transformation from prepared adduct **C** to the corresponding desired benzofuran. Although the reason why hydrate coordinated iron plays an important role in the oxidative coupling step was unknown, this approach was an efficient alternative pathway to construct biologically important 3-carboxylate benzofurans.

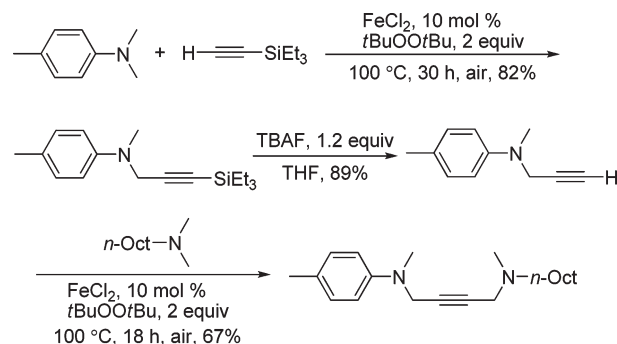
### 6.3. CDC between $sp^3$ and $sp$ C–H Bonds

Besides 1,3-dicarbonyl compounds, electron-rich arenes, as well as alkene derivatives, terminal alkynes were also investigated as a carbon nucleophile in iron-catalyzed oxidative cross-coupling. Li and

**Scheme 44.** Tentative Mechanism of Iron-Catalyzed Tandem Oxidative Coupling and Annulation



**Scheme 45.** Chemoselective  $FeCl_2$ -Catalyzed Oxidative Couplings with Two Different Tertiary Amines

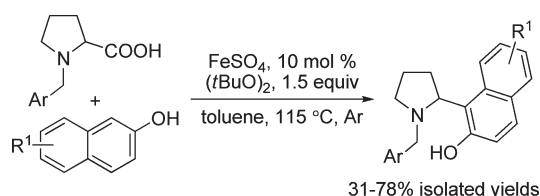


co-workers reported the beautiful example to realize the direct alkynylation of  $sp^3$  C–H bonds adjacent to the N atom of both aromatic and aliphatic tertiary amines with terminal alkynes. This transformation was carried out solvent free in the presence of  $FeCl_2$  as a catalyst with DTBP as an efficient oxidant in excellent efficacy.<sup>95</sup> A silyl group could be applied for protecting the other side of the terminal alkyne, which provided an efficient method to construct asymmetric 1,4-propargylic diamine by double CDC processes (Scheme 45). Similarly, this process supposedly went through the iron-catalyzed SET process to generate the iminium intermediate, which was quenched by alkynyl carbon anion to yield the desired products.

## 7. C–C BOND FORMATION VIA DECARBOXYLATIVE COUPLING

Carboxylic acids exist in a variety of organic compounds. Due to their ready availability, lower toxicity, and low cost, transition-metal-catalyzed intermolecular/intramolecular decarboxylative couplings of carboxylic acids directly as starting materials were developed by Goossen,<sup>96</sup> Myers,<sup>97</sup> Tunge,<sup>98</sup> and others. Recent advances indicated that the cross-coupling with the combination of decarboxylation and direct C–H transformation showed great potential. Among those decarboxylation processes, late transition metals showed their advantages.<sup>99</sup> To approach the potential application of these methods, the strategies which can provide less cost, generate less waste, and tolerate more substrates will be

**Scheme 46. Iron-Catalyzed Decarboxylative C(sp<sup>3</sup>)–C(sp<sup>2</sup>) Coupling of Proline Derivatives and  $\beta$ -Naphthols**



attractive. One of the possible improvements is the replacement of expensive transition metals by cheap first row transition metals, such as iron.

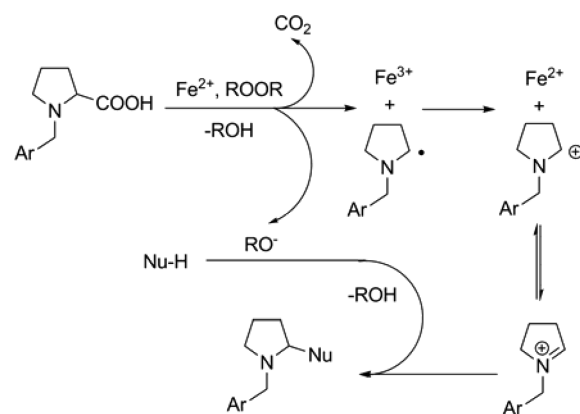
To approach such a challenge, iron was selected to catalyze the decarboxylation to construct a C–C bond. Actually, this field was extremely undeveloped, and to date, only one successful example was reported by Li and co-workers. In their report, proline derivatives went through the novel iron-catalyzed decarboxylative process, followed by the construction of a C–C bond through the coupling with different naphthols.<sup>100</sup> For example, by using *N*-benzyl proline and  $\beta$ -naphthol as starting materials, the desired C(sp<sup>2</sup>)–C(sp<sup>3</sup>) bond was constructed in the presence of various iron salts as catalysts and peroxide as the proper oxidant. In this transformation, the isolated yield was up to 78% (Scheme 46). Other than  $\beta$ -naphthols, electron-rich  $\alpha$ -naphthols and indoles were also suitable nucleophiles to fulfill this decarboxylative cross-coupling.

Supposedly, the reaction pathway was initiated from the homolysis of peroxides promoted by iron salts as reported.<sup>101</sup> After the homolysis, *tert*-butyl radical trapped the hydrogen of the proline to initiate the decarboxylation. The formed 2-pyrrolidinyl radical could be further oxidized by Fe<sup>3+</sup> generated in situ, and then 2-pyrrolidinium cation species was generated as a key intermediate. At the same time, Fe<sup>2+</sup> was regenerated. This intermediate 2-pyrrolidinium cation was further subjected to nucleophilic attack by electron-rich arenes to afford the coupling products (Scheme 47). This transformation exhibited its great potential for the promising synthetic applications as a beautiful example of the improvement of amino acid decarboxylative coupling.

## 8. C–C BOND FORMATION VIA ALKENES INSERTION

As discussed above, after the formation of a radical or cationic intermediate through iron-catalyzed SET processes, various electron-rich organic compounds could be supposedly applied to quench such intermediates to form C–C bonds as well as C-heteroatom bonds. Actually, cross-coupling of C–H with alkene derivatives was developed as a successful example.<sup>102</sup> As mentioned above, a stoichiometric amount of hydrogen acceptors, such as peroxides or benzoquinones, is essential to facilitate such a “cross dehydrogenative coupling” (CDC) process. Obviously, another feasible design was posed to execute the direct addition of C–H bonds toward unsaturated organic species. Presumably, if unsaturated organic compounds such as alkenes, alkynes, and allenes are introduced in the absence of hydrogen acceptors, the radical intermediates might readily add to multiple C–C bonds to form new C–C bonds with the generation of new radical intermediates, which can be quenched by the proton or hydrogen generated at the initiating step. If this ideal process took place, the reaction would result in the insertion of unsaturated

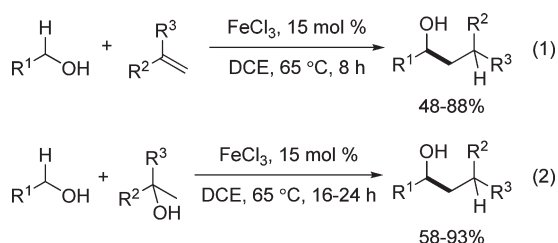
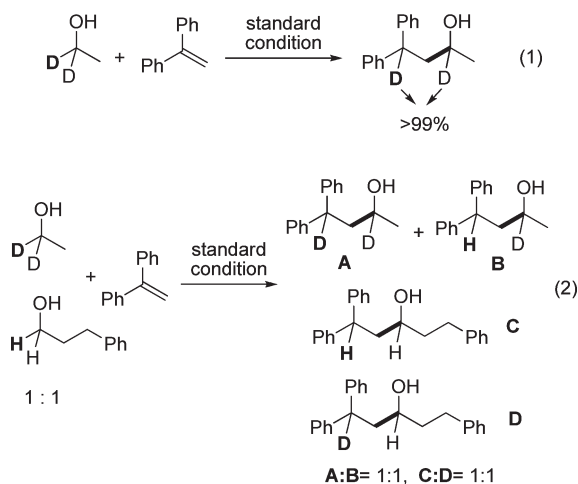
**Scheme 47. Proposed Mechanism for Iron-Catalyzed Decarboxylative Coupling**



compounds into C–H bonds in a greener and more efficient way.

In fact, Tu and co-workers developed the first significant example based on this reasonable design.<sup>103</sup> As demonstrated above, sp<sup>3</sup> C–H bonds adjacent to heteroatoms are relatively active in various iron-catalyzed processes. In Tu's studies, they chose alcohols as their starting point to pursue their goals with proper alkenes. In model studies, 3-phenylpropanol and 1,1-diphenylethylene were selected. They found that alkene was successfully inserted into C–H at the  $\alpha$ -position of alcohol in high efficacy. During this transformation, FeCl<sub>3</sub> exhibited higher catalytic activity than other iron salts, such as FeCl<sub>2</sub>, FeCl<sub>3</sub>·6H<sub>2</sub>O, Fe(ClO<sub>4</sub>)<sub>3</sub>·9H<sub>2</sub>O, etc. Notably, DCE was the only efficient solvent to facilitate this addition. In some cases, DCE could even be used to promote the efficacy as an additive, which suggested that DCE was essential for this transformation. Moreover, common ligands in iron chemistry, such as TMEDA, NEt<sub>3</sub>, and DACH (*trans*-1,2-diaminocyclohexane), did not significantly improve the yield. Under the developed conditions, various alkenes and primary alcohols could undergo the reaction in moderate to excellent yields (Scheme 48, eq 1). Notably, alkenes could be in situ generated from tertiary alcohols under the coupling conditions but with a longer reaction time (Scheme 48, eq 2).

Additional experiments were carefully conducted to elucidate the possible reaction pathway. Under the standard reaction conditions, as noted, no desired hydroacylation reaction was observed in the presence of PhCH<sub>2</sub>CH<sub>2</sub>CHO instead of the corresponding alcohol. This result excluded the possible “oxidation/hydroacylation/reduction” or “transfer-hydrogenative coupling” process. Deuterium-labeling experiments were further surveyed to unveil the hydrogen transfer. The results indicated that the proton at the final product entirely came from C–H bonds adjacent to the hydroxyl group (Scheme 49, eq 1). The deuterium-labeled crossover experiment also showed a statistical distribution in the products (Scheme 49, eq 2). All those results met the discretely intermolecular hydrogen-transfer process from alcohol to alkene.<sup>104</sup> Therefore, a possible mechanism was proposed in Scheme 50. After iron-initiated cleavage of the sp<sup>3</sup> C–H bond adjacent to the oxygen of alcohols, a radical pair **B** formed, followed by simultaneous free-radical addition and disassociation to afford both [Fe<sup>IV</sup>]–H and a free-radical species

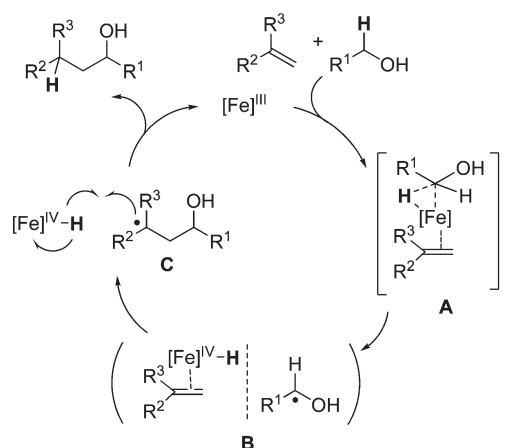
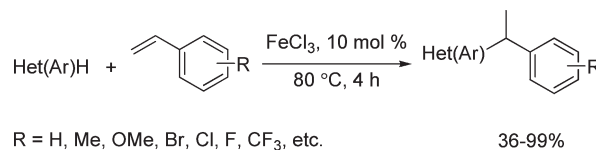
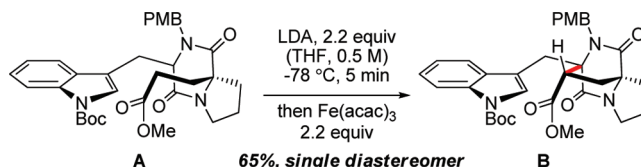
**Scheme 48. Cross-Coupling Reaction of Primary Alcohols with Various Alkenes or Tertiary Alcohols****Scheme 49. Deuterium-Labeled Experiments**

C. Subsequently, the iron hydride intermediate underwent an outer-sphere-type hydrogen transfer to give the coupling product, thus regenerating the iron-catalyst for the next catalytic cycle.

Another example of iron-catalyzed C—C bond formation with alkenes was the hydroarylation of styrenes, and a C(sp<sup>2</sup>)—C(sp<sup>3</sup>) bond could be constructed via Fe-catalysis, which was recently reported by Beller and co-workers.<sup>105</sup> Most likely, this developed process might go through the traditional Friedel–Crafts pathway rather than the aforementioned free radical process. But anyway, this method offered an easier and more practical approach to construct substituted 1,1-diaryllkanes and 1-aryl-1-heteroarylalkanes (Scheme 51).

## 9. OXIDATIVE COUPLING OF DIFFERENT C—H BONDS AND RELATED APPLICATIONS

Iron-catalyzed C—H transformations represent a kind of novel and “green” methodologies, especially in C—C bond formation, which remains the cornerstone in organic synthesis. However, in most cases, the C—C bond formation process involves a free radical pathway, which to some extent increases the difficulty in controlling the selectivity and efficiency. The design or selection of substrates would be critical for a radical process. Besides the iron-catalyzed C—H oxidation methods developed by White, a few examples have been reported in the aspect of iron-catalyzed C—C bond formation processes in total synthesis. However, some results involving iron-mediated C—H transformation in a stoichiometric manner to a construct C—C bond as a key step in

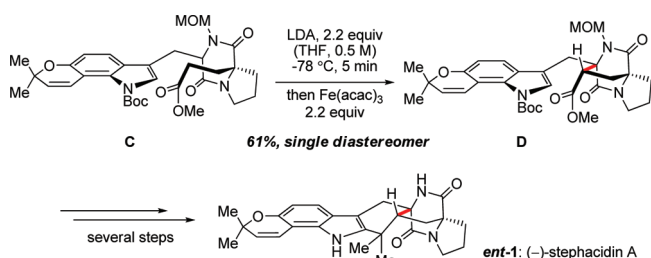
**Scheme 50. Proposed Mechanism for Iron-Catalyzed Reaction of Primary Alcohols with Alkenes****Scheme 51. Iron-Catalyzed Hydroarylation of Styrenes****Scheme 52. Iron-Mediated Intramolecular Oxidative Heterocoupling**

a total synthesis have been reported by Baran. Although stoichiometric iron salts were used as oxidants at this stage, the intramolecular oxidative coupling of carbonyl compounds, as well as the intermolecular heterocoupling of enolates, has been well studied and successfully introduced into the total synthesis of avrainvillamide and stephacidins.

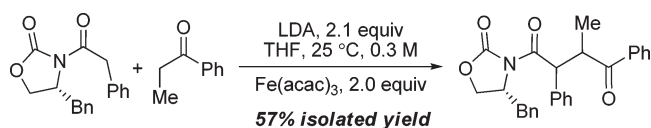
The iron-mediated direct coupling of indoles with carbonyl compounds was first found in the synthesis process of hapalindole and fischerindole. Iron salts-mediated oxidative coupling of indoles and carvones was realized in spite of a very low yield.<sup>106</sup> Then Baran and co-workers carried out an intensive investigation of the intramolecular oxidative C—C bond formation.<sup>107</sup> In the optimization of model molecule A, Fe(acac)<sub>3</sub> was the most efficient oxidant and the conditions were described in Scheme 52. The cyclization product B was obtained in 65% isolated yield as a single diastereomer.

From the model studies, this iron-mediated oxidative coupling was successfully used in the total synthesis of *ent*-stephacidin A. From the fragment C, the same conditions as those for model

**Scheme 53. Application of Iron-Mediated Intramolecular Oxidative Heterocoupling in the Total Synthesis of *ent*-Stephacidin A**



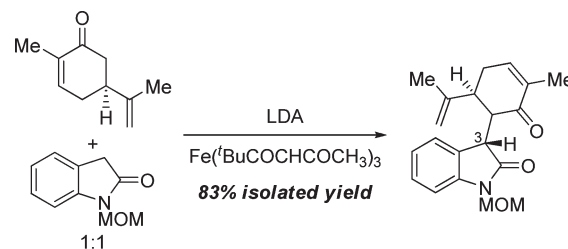
**Scheme 54. Iron-Mediated Oxazolidinone–Propiophenone Heterocoupling**



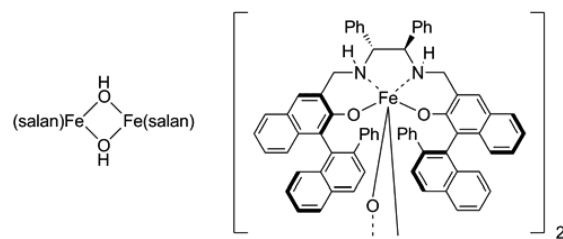
studies were used, and product **D** was obtained in 61% isolated yield as a single diastereomer (Scheme 53). Such a C–C bond formation step was critical for the construction of the bicyclic core of stepacidin alkaloids and provided an evolutive strategy for the synthesis of the stephacidin family. This iron-mediated method was reliable and proceeded in good yield even on a preparative scale with a high stereoselectivity. Furthermore, the hypothesis about the selectivity was proposed as follows: the chemoselectivity of this reaction was controlled by the unique oxidation potential of the iron-based oxidant, and the stereoselectivity was achieved by an iron-chelated transition state.

From the discovery and development of oxidative coupling of indoles with carbonyl compounds, as well as the intramolecular oxidative heterocoupling, a further extensive investigation was focused on the oxidative intermolecular coupling of two different carbonyl species.<sup>108</sup> There are great challenges in intermolecular oxidative heterocoupling, especially the chemoselectivity. In the process, many possible side reactions, such as homodimerization, homo-Claisen condensation, cross-/homo-aldol condensation, overoxidation, dehydrogenation, and  $\alpha$ -oxidation, would compete with the desired heterocoupling. Actually, the homodimerization of enolates has already been widely studied and represents an excellent method for succinate synthesis. Claisen condensation and aldol reaction are both important named reactions in organic chemistry and can be easily conducted under simple conditions. It seems troublesome to avoid the generation of those byproducts. Based on a series of meticulous analysis and optimization, the desired heterocoupling could be achieved using iron or copper salts as the oxidant. Take iron-mediated heterocoupling of oxazolidinone–propiophenone for example. The desired product was obtained in 57% isolated yield in THF at 25 °C (Scheme 54). The substrate scope of this method was quite broad. However, moderated yields were obtained and low diastereoselectivities could hardly have been avoided. Notably, the formation of quaternary centers from this

**Scheme 55. Oxidative Oxindole Coupling**



**Scheme 56. Structure of Iron(salan) Complex**



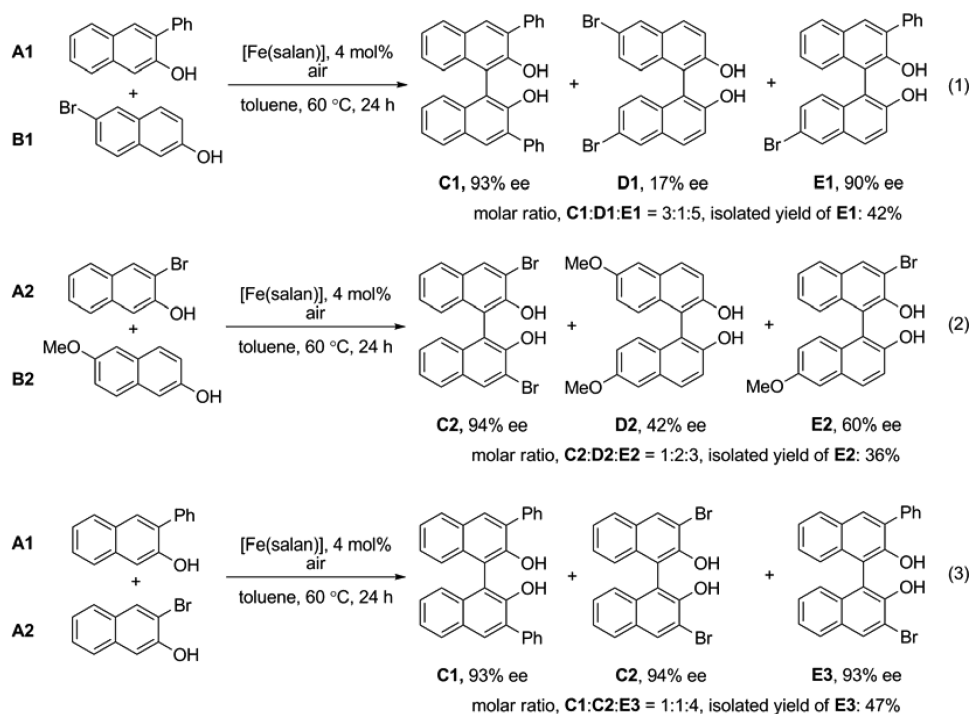
method remains a limitation. Extensive mechanistic studies indicated that a nontemplate heterodimerization pathway was involved in iron(III)-based couplings, which was different from the metal-chelated single electron transfer process in the case of copper(II).

In the family of natural product hapalindoles, fischerindoles, and welwitindolinones, a unique structural unit of an indole-based heterocycle with a monoterpene unit tethered at the C3 position was notable as a core of these molecules. During the studies of construction of this core unit, an oxidative coupling of carvones and indinones was developed as an alternative strategy.<sup>109</sup> When an acetylacetonate-type ligand  $t\text{BuCOCHCOCH}_3$  was used on the iron, the reaction was carried out efficiently, providing the desired product in 83% isolated yield (1:1 mixture of diastereomers at C3). Both coupling partners were used in equimolar quantities (Scheme 55).

Very recently, Katsuki reported an important iron-catalyzed oxidative cross-coupling of 2-naphthols and its synthetic application in constructing  $C_1$ -symmetric BINOLs.<sup>110</sup>  $C_2$ -symmetric BINOL derivatives have already been widely used as chiral auxiliaries.<sup>111</sup> On the other hand,  $C_1$ -symmetric BINOLs are also considered to be potentially good chiral auxiliaries, and recent seminal studies have given some indication.<sup>111a,112</sup> Obviously, the synthesis of this kind of BINOLs was still very difficult. Asymmetric aerobic oxidative cross-coupling between two different 2-naphthols should be the simplest and most direct method; however, only one copper-mediated example preferentially provided the oxidative cross-coupling product with good enantioselectivity.<sup>113</sup> Katsuki started their research from asymmetric aerobic oxidative homocoupling with an iron(salan) complex (Scheme 56) and developed an oxidative cross-coupling reaction with a broad substrate scope.

The author expected and finally certified that a combination of a 2-naphthol bearing a substituent at C3 and a less electron-rich 2-naphthol either with or without a substituent at C3 would undergo the cross-coupling in high enantioselectivity. For example, both the

Scheme 57. Enantioselective Iron(salan)-Catalyzed Asymmetric Oxidative Coupling of 2-Naphthols



reaction between the two naphthols **A1** and **B1** (Scheme 57, eq 1) and that between the two naphthols **A2** and **B2** (Scheme 57, eq 2) preferentially gave the cross-coupling products. The ee value of the cross-coupling product **E1**, in which the C3 substituent exists in the electron-rich naphthol moiety, was as high as 90%, while the ee value of the product **E2** without the C3 substituent in the electron-rich naphthol moiety was moderate, only 60%. This reaction could also be successfully applied to the oxidative cross-coupling between the electron-rich and -poor 2-naphthols both with a C3 substituent (Scheme 57, eq 3).

A more plausible mechanism for this cross-coupling reaction was a typical radical-anion coupling, which was proven by a series of systematic investigations, especially the kinetic studies. This cross-coupling reaction possesses a wider substrate scope than that of the previous reports,<sup>113</sup> which enabled us to establish a highly enantioselective aerobic oxidative cross-coupling method for the preparation of  $C_1$ -symmetric BINOLs.

## 10. CONCLUSION AND PERSPECTIVE

Iron-catalyzed organic chemistry is an ancient chemistry but again blossoms out nowadays due to its attractive advantages and promising application in organic synthesis, especially in catering for the concept and demand of “green chemistry”. Iron catalyzed direct C–H transformation meets the requirement of high efficacy, low waste, and sustainable process in synthetic chemistry from the whole society. Starting from early this century, numerous novel methodologies according to these points have been developed, and great progress has been made in exploring both new synthetic applications and catalytic pathways. A great breakthrough of iron-catalyzed oxidation of unactivated  $\text{sp}^3$  C–H bonds was achieved after Gif, Fenton, and nonheme mimic chemistry were well developed. In many other aspects, significant

developments were made, such as decarboxylative coupling, alkene insertion, cross coupling with organohalides and organometallic reagents, as well as cross-dehydrogenative coupling (CDC). In most cases, an iron-promoted single-electron transfer (SET) process was considered as a fundamental initiating step to facilitate transformations.

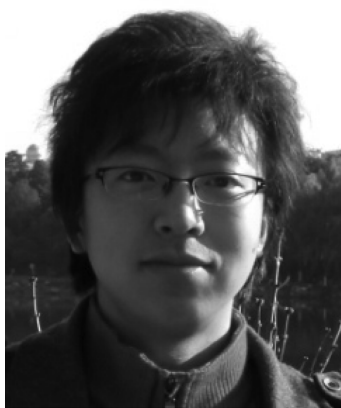
In spite of the great significance and brilliant prospects, the studies of iron-catalyzed direct C–H transformations remain challenging. Undoubtedly, the special efficiency, selectivity, and tolerance of functional groups indicated their uniqueness and applicability, and the experimental observation and obtained results could provide some suggestion on the mechanism. Further efforts to understand the nature of such transformations were necessary. For example, due to the intrinsic feature of Fe elements, various valences of Fe species might exist in the oxidative reaction conditions, and the exact catalytic species to process those transformations were still unknown. Rare examples of structurally defined Fe-containing intermediates have been traced to support the proposed catalytic pathways. Meanwhile, the extension of the substrates scope as well as the improvement of efficiency and practicality is still at the primary stage. However, iron-catalyzed transformation has already been kaleidoscopic and flourishing, and the achievements encourage the blossoming-out of the new synthetic methodologies by the unique features and advantages of iron catalysis. With chemists' further investigation, the chemistry of iron catalysis would find their positions and great honor in synthetic chemistry.

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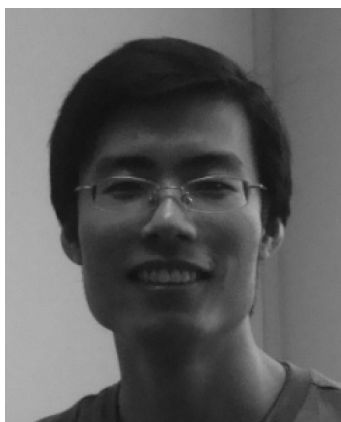
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