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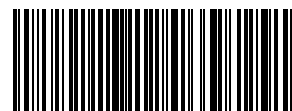
TUTORIAL REVIEW

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Iron-catalysed carbon–heteroatom and heteroatom–heteroatom bond forming processes

Arkaitz Correa, Olga García Mancheño and Carsten Bolm*

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Given its ready availability, low price and environmentally friendly character, iron is an attractive and often advantageous alternative to other transition metals in the field of catalysis. This *tutorial review* summarises recent progress in the development of novel and practical iron-catalysed reactions with a particular focus on those which provide access to new carbon–heteroatom and heteroatom–heteroatom linkages. It shall be of interest for both the academic as well as the industrial community.

1. Introduction

Owing to the prevalence of carbon–heteroatom (C–X) and heteroatom–heteroatom (Y–X) bonds in organic compounds being relevant in biological, pharmaceutical, and material sciences, the development of environmentally friendly, safe and reliable transition metal-catalysed methods for their construction constitutes a major goal of high practical value for modern chemistry and chemical industry. In this respect, iron is an ideal transition metal, given its low price, non-toxicity and environmentally benign character, which often offers notable advantages in terms of sustainable chemistry and represents hence an attractive alternative to other commonly used transition metals. Indeed, in the last few years the use of easy-to-handle and generally air-stable iron salts for such purposes has increased considerably and a plethora of iron-catalysed methods is now available providing new challenging possibilities in organic synthesis.

In 2004 we summarised the most important transformations catalysed by iron salts in organic synthesis.¹ Since then, an exponential number of papers involving novel iron catalysts

have appeared. The main objective of this review is to describe the most relevant developments, which allow access to valuable carbon–heteroatom and heteroatom–heteroatom linkages being of interest for industrial and academic chemists. Although impressive progress has been recently made in the field of iron-catalysed C–C cross-couplings² and hydrogenations,³ such transformations as well as the chemistry of ferrocenes and iron porphyrins are beyond the aim of this overview. The review will be divided into sections according to the nature of the new bond generated in the iron-catalysed process.

2. Carbon–heteroatom bond formation

2.1. Carbon–nitrogen bond formation

N-Arylations. The metal-catalysed reaction between a nitrogen-nucleophile and an aryl halide leading to a new C–N linkage is often described as an *N*-arylation reaction. In particular, the *N*-arylation of nitrogen-containing heterocycles is recognised as one of the most powerful means for the C–N bond formation due to the paramount industrial importance of the resulting *N*-aryl heterocycles. Traditionally, such coupling reactions have been performed with palladium and copper-catalysts, but despite the efficiency of the latter protocols the development of alternative cost-efficient catalysts is highly desirable. Along these lines, Taillefer and co-workers reported a novel iron–copper cooperative catalysis to assemble *N*-aryl heterocycles by *N*-arylation of several heterocycles with aryl halides.⁴ Interestingly, the combination of 10 mol% of CuO and 30 mol% of Fe(acac)₃ proved rather effective for the arylation of pyrazole, imidazole, pyrrole, triazoles, indole and pyrrolidinone. The experimental conditions involved the use of Cs₂CO₃ as base and DMF as solvent with aryl iodides and bromides as arylating agents at temperatures ranging from 90 °C to 120 °C. Furthermore, encouraging results were obtained when an activated aryl chloride was employed at higher temperatures (140 °C). Alternatively, a solvent-free iron–copper co-catalysed *N*-arylation protocol of various triazoles and imidazoles under air atmosphere with arylsilanes as electrophilic counterparts was developed by Li *et al.*⁵ In the

Institut für Organische Chemie der RWTH Aachen University,
Landoltweg 1, D-52056 Aachen, Germany. E-mail:
carsten.bolm@oc.rwth-aachen.de; Fax: +49 (241) 8092391;
Tel: +49 (241) 8094675



From left to right: Dr Arkaitz Correa,
Dr Olga García Mancheño, Prof. Dr Carsten Bolm

latter case, comparatively milder reaction conditions with a lower catalyst loading (3 mol% of Cu and 3 mol% of FeCl₃) and a reduced temperature (50 °C) were required. The potential drawback of both methodologies is the requirement to use two metals in the catalyst system.

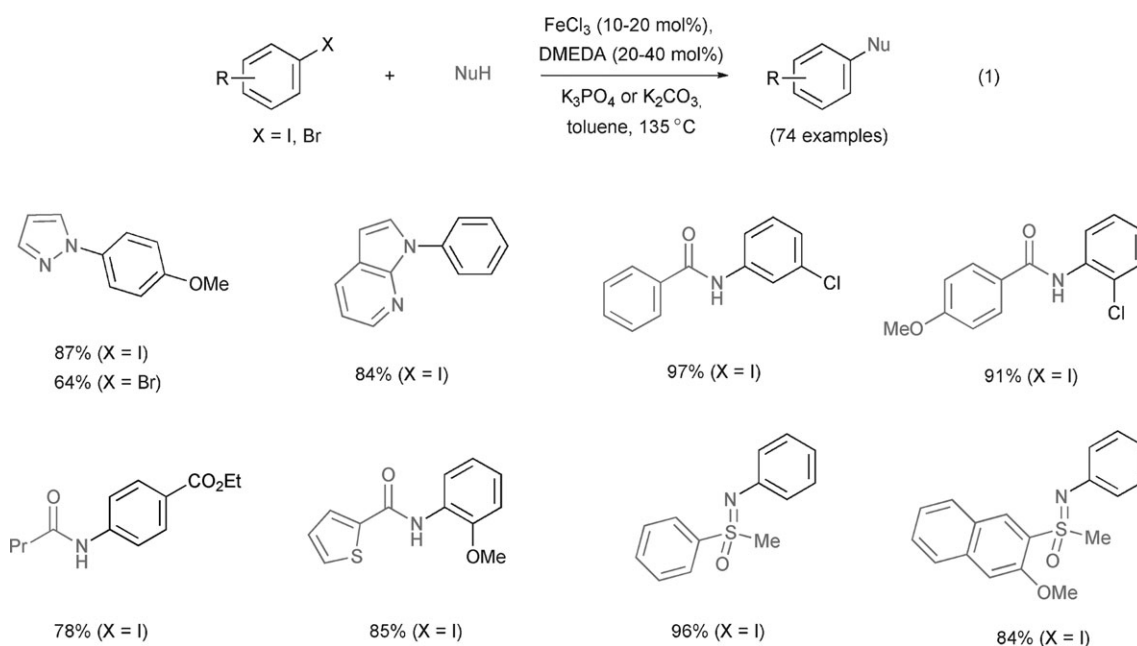
Recently, Correa and Bolm reported alternative *N*-arylations of nitrogen nucleophiles with aryl halides utilising exclusively iron as the metal of choice.⁶ The key finding for this novel transformation was the catalytic effect of a combination of 10 mol% of inexpensive FeCl₃ and 20 mol% of *N,N'*-dimethylethylenediamine (DMEDA) as a chelating ligand. The nature of the base and solvent as well as the temperature played a determinant role in the coupling process, and the best experimental conditions involved toluene as solvent and K₃PO₄ or K₂CO₃ as base at 135 °C. This C–N coupling protocol represented a major breakthrough in the field of *N*-arylations due to its generality and versatility. Thus, in addition to some *N*-heterocycles (pyrazole, indole and azaindole) various other nitrogen nucleophiles such as primary amides (aromatic, aliphatic and heteroaromatic substrates)⁷ and sulfoximine derivatives⁸ efficiently underwent the target coupling process. Furthermore, a number of heterocycles such as oxindole and quinolinone derivatives became accessible by iron-catalysed intramolecular ring closures of iodo-substituted arenes with primary amide moieties.⁷ This iron-catalyst appears promising for industrial-scale synthesis and further research could deliver operationally simple and cost-effective processes in the near future. The main limitation of the system relates to the employment of aryl iodides as the electrophilic partners and only a few successful examples with aryl bromides have been reported so far. Scheme 1 (eqn (1)) summarises this approach and illustrates a few important examples.

Hydroaminations. Another important class of C–N bond forming reactions is the addition of an amino group (N–H) to

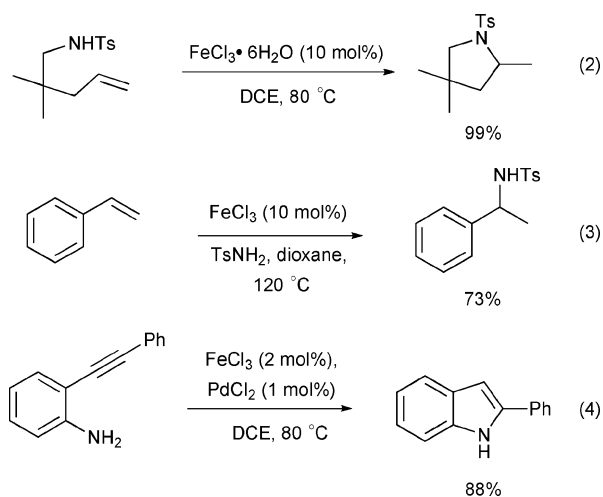
either an alkene or an alkyne. These so-called hydroaminations are particularly attractive from the standpoint of green chemistry because they generally display high atom economy. A large number of transition metal complexes (including lanthanide-, titanium-, zirconium-, platinum- and ruthenium-based ones) are known to catalyse these C–N bond forming processes. In view of the high price and toxicity of some of these metals, the employment of cheaper and more environmentally friendly iron catalysts in hydroamination reactions has recently attracted attention.

In 2006 the first iron-catalysed intramolecular hydroamination of unactivated olefins was published by Komeyama, Takaki *et al.*,⁹ who showed that the activity of the iron system was superior to that of conventional transition-metal catalysts (Scheme 2, eqn (2)). Indeed, the use of catalytic amounts of FeCl₃·6H₂O provided better results than CoCl₂, NiCl₂, ZnCl₂, CuCl₂, Cu(OTf)₂ or AgOTf in the hydroamination with tosylamides. The solvent strongly affected the reaction outcome, and 1,2-dichloroethane proved to be the solvent of choice when performing the process at 80 °C under air. Moreover, differently 1,2-disubstituted aminoolefins afforded the corresponding *N*-heterocycles in almost quantitative yields, and a high tolerance of olefinic substrates containing iodides was observed. Likewise, the authors noted that the construction of five-membered rings was more favorable than that of six- and seven-membered rings.

The first intermolecular examples of an iron-catalysed hydroamination of alkenes were described by Prim, Campagne and co-workers.¹⁰ In their preliminary studies the authors observed that 10 mol% of FeCl₃ efficiently catalysed the hydroamination of certain styrenes with deactivated nitrogen nucleophiles such as sulfonamides, benzamides or anilines bearing electron-withdrawing groups (Scheme 2, eqn (3)). Whereas the presence of electron-donating groups at the arene ring of the styrenes was well tolerated, electron-withdrawing moieties entirely inhibited the hydroamination reaction.



Scheme 1 Iron-catalysed *N*-arylations of nitrogen nucleophiles.



Scheme 2 Examples of iron-catalysed hydroaminations.

Furthermore, this method had severe limitations in the fact that only terminal olefins were reactive and hence α - or β -substituted styrenes furnished the hydroaminated compounds in much lower yields. Subsequently, Takaki and co-workers reported one isolated example of an intermolecular hydroamination (together with a general method for the addition of carboxylic acids to olefins, which will be discussed in a later section devoted to C–O bond formation). These authors found that in the presence of $\text{Fe}(\text{OTf})_3$, generated *in situ* by mixing 2 mol% of FeCl_3 and 6 mol% of AgOTf , the hydroamination of norbornene with TsNH_2 proceeded quantitatively.¹¹

Recently, Prim, Campagne and co-workers described iron–palladium cooperative catalysis in the assembly of important indole derivatives by intramolecular hydroamination of alkynes (Scheme 2, eqn (4)).¹² The catalyst screening performed with alkynylamines as model substrates revealed that both metals were required for the annulation to occur. The employment of low amounts of FeCl_3 (2 mol%) and PdCl_2 (1 mol%) led to the formation of indoles in high yields when carrying out the reaction in dichloroethane at 80 °C in flasks open to air. The authors suggested that the iron species together with oxygen would serve as an oxidiser for the *in situ* regeneration of the palladium catalyst, allowing completion of the Pd^0 – Pd^{II} catalytic cycle. This hypothesis was verified by utilising 1 mol% of PdCl_2 in combination with other oxidants such as CuCl_2 or benzoquinone, which led to similar results.

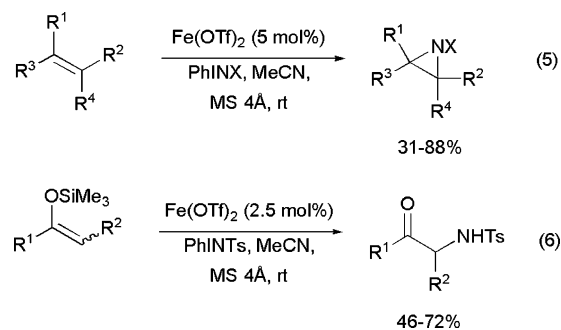
Aziridinations. Nitrene transfer to olefins is another important C–N bond forming process, which gives rise to synthetically useful building blocks for a wide range of nitrogen-containing compounds. Although aziridination reactions catalysed, for instance, by copper or rhodium complexes are well-established,¹³ in the past years iron species have been added to the relatively long list of catalysts found so far.

In 2003 Hossain and co-workers reported useful applications of the iron Lewis acid $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2(\text{THF})]^+[\text{BF}_4]^-$ in the aziridination of styrenes and stilbenes with the iminoiodane PhINTs.¹⁴ A year later, Avenier and Latour demonstrated that a mixed-valent diiron complex could catalyse the aziridination of several olefins (styrene, cyclooctene and

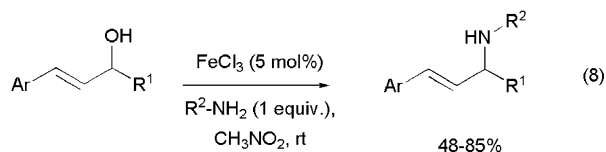
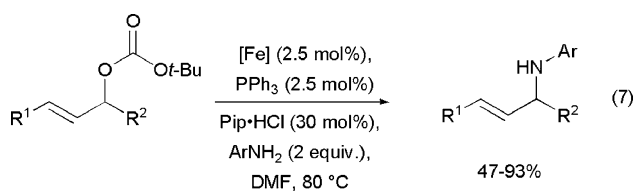
1-hexene) with PhINTs.¹⁵ Comparing both protocols, the major disadvantage of the latter one is the need for a large excess of olefin (>25 equiv. *vs.* PhINTs) to ensure acceptable product yields. In contrast, the former method involves the use of much lower olefin amounts (2–5 equiv.). Very recently, Halfen and co-workers reported the catalysed aziridination of alkenes with PhINTs using mononuclear non-heme iron(II) complexes.¹⁶ They observed that such iron catalysts had higher activity than the complex $\text{Fe}(\text{OTf})_2\cdot 2\text{MeCN}$ in the aziridination of styrene, allowing the process to take place using just 5 equiv. of the olefin (*vs.* PhINTs). Conversely, unlike the protocol developed by Avenier and Latour, aliphatic substrates such as 1-hexene underwent the aziridination reaction in very low yields.

Prompted by these results, we have recently reported on our early attempts to effect iron-catalysed aziridination reactions.¹⁷ It was demonstrated that iron(II) triflate efficiently catalysed the aziridination of aromatic and certain aliphatic olefins with both pre-formed and *in situ* prepared iminoiodanes as nitrene transfer reagents (Scheme 3, eqn (5)). In all cases, an excess of substrate (5–20 equiv.) was required to achieve reasonable conversions. Importantly, encouraging results were obtained when attempting asymmetric aziridinations in the presence of chiral ligands. Thus, among various tridentate ligands tested in the aziridination of styrene, C_2 -symmetric bis(oxazoline) derivatives, known as box ligands, were most effective, leading to the corresponding aziridine in good yield and low albeit promising enantiomeric excess (up to 40% ee). In addition, this iron-catalysed aziridination protocol proved suitable for the aziridination of several silyl enol ethers, affording the target α -*N*-tosylamido ketones by subsequent aziridine ring opening (Scheme 3, eqn (6)).

Allylic aminations. Allylic substitutions are extremely powerful reactions in organic synthesis and of particular interest is the allylic amination owing to the importance of the resulting nitrogen compounds. The work concerning oxidative iron-catalysed aminations of unactivated olefins published simultaneously by the groups of Jørgensen¹⁸ and Nicholas¹⁹ was covered in our previous general overview of iron catalysis and hence will not be commented on again herein. The only iron-catalysed process of this type reported since then concerns the regioselective allylic amination of allyl carbonates using $[\text{Bu}_4\text{N}][\text{Fe}(\text{CO})_3(\text{NO})]$ as a catalyst developed by Plietker.²⁰ In connection with his previous work



Scheme 3 Iron-catalysed aziridinations.



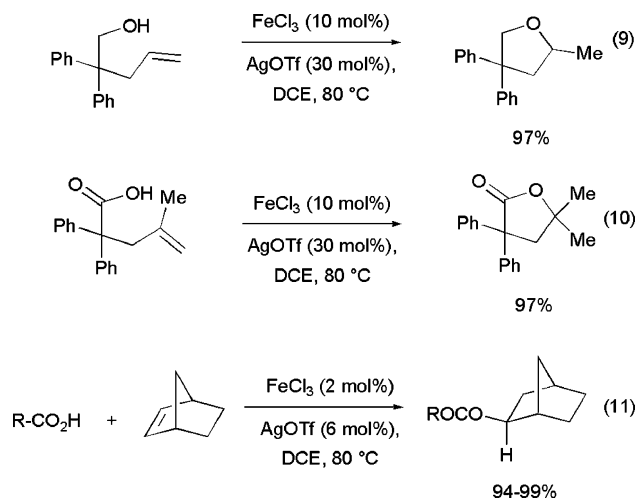
Scheme 4 Iron-catalysed allylic aminations and amidations.

using that catalyst in the allylic alkylation of allyl carbonates with C-nucleophiles,²¹ Plietker described a practical C–N bond forming process by utilising anilines as nucleophiles in such substitution processes (Scheme 4, eqn (7)). He observed that when treating primary and secondary allyl carbonates with differently substituted anilines in the presence of the aforementioned iron-catalyst, the new C–N bond was in all cases formed selectively at the carbon atom of the allyl moiety bearing the leaving group. Unlike when employing malonic acid derivatives as nucleophiles, catalytic amounts of piperidinium chloride acting as a buffer along with an increase in the substrate concentration proved necessary in the allylic aminations in order to avoid catalyst decomposition. In accordance with the proposed mechanism,²² the iron-catalysed allylic aminations of enantiomerically pure allyl carbonates proceeded with almost complete chirality transfer and retention of configuration.

In 2008 an advantageous iron-catalysed direct substitution of benzyl and allylic alcohols with structurally varied primary amides (benzamide, *p*-toluenesulfonamide, acetamide and acrylamide) was published.²³ Jana and co-workers found that environmentally friendly FeCl₃ allowed such transformations to occur under very mild reaction conditions involving the use of nitromethane as solvent at room temperature (Scheme 4, eqn (8)).

2.2. Carbon–oxygen bond formation

Addition reactions. The addition of oxygenated moieties such as alcohols or carboxylic acids to unactivated olefins represents a synthetically useful tool and a straightforward access towards new C–O bonds. Despite the fact that other metals are known to facilitate such transformations, iron salts have been recently employed for such synthetic purposes. In this respect, Takaki, Komeyama *et al.* developed an efficient iron-catalysed intramolecular hydroalkoxylation of alkenes utilising *in situ* formed Fe(OTf)₃ prepared by combining FeCl₃ and AgOTf (Scheme 5, eqn (9)).²⁴ They observed that its catalytic activity, which was clearly superior to that of FeCl₃, depended on the anion of the silver salt. Thus, with AgOTf as an additive the reaction proceeded in shorter reaction times and higher yields than with AgClO₄ or AgBF₄. Furthermore, the same iron catalyst was employed for the addition of carboxylic acids to olefins and was found to be more effective than other related transition-metal catalysts such as Cu(OTf)₂ or Zn(OTf)₂ (Scheme 5, eqn (10)).¹¹ Besides the intramolecular

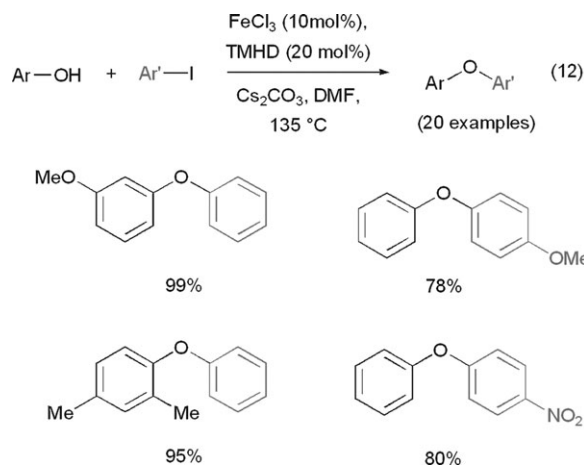


Scheme 5 Examples of FeCl₃-catalysed additions of alcohols and carboxylic acids to olefins.

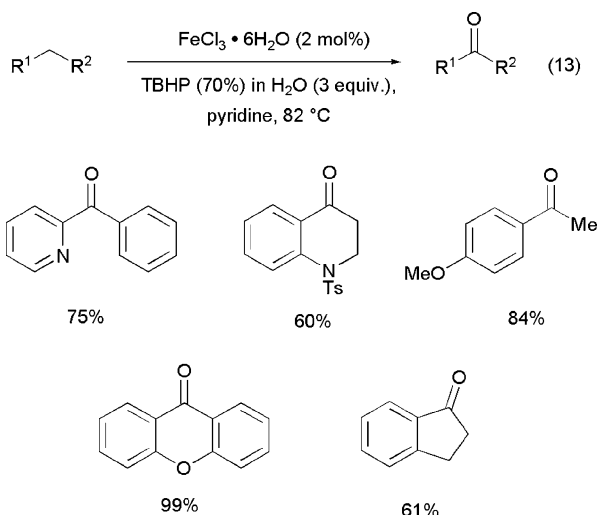
heterofunctionalisation examples, *exo*-selective intermolecular addition processes of both aromatic and aliphatic carboxylic acids to norbornene were reported (Scheme 5, eqn (11)). It is remarkable that the same iron catalyst, Fe(OTf)₃, also assisted the intermolecular addition of other nucleophiles such as amines and diketones to norbornene, leading to the addition products by C–N and C–C bond formation, respectively.

O-Arylations. Another iron-catalysed C–O bond forming process recently reported is the cross-coupling of phenols with aryl halides. Also in these *O*-arylations, simple iron complexes were found to be applicable.²⁵ Screening experiments confirmed that the interplay among solvent, base and catalyst had a determinant role in the reaction outcome. Thus, in this case the success of the process relied on the use of FeCl₃ in combination with a diketonic ligand (2,2,6,6-tetramethyl-3,5-heptanedione, TMHD), which had to be used in the presence of Cs₂CO₃ and DMF at 135 °C. Under such conditions, a wide range of important diaryl ethers were obtained by catalysed couplings of phenols and aryl iodides (Scheme 6, eqn (12)).

C–H oxidations. The development of novel oxidation processes involving green oxidants is one of the most pressing



Scheme 6 Iron-catalysed *O*-arylations.



Scheme 7 Iron-catalysed benzylic oxidations.

goals in organic synthesis and iron catalysts proved useful in several applications of such type. Most challenging is the direct oxidation of unfunctionalised substrates bearing aliphatic (sp^3) C–H bonds. Along these lines, the oxidation of cycloalkanes and alkylarenes applying catalytic amounts of readily available $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and H_2O_2 in acetonitrile at room temperature has recently been reported.²⁶ The chemoselectivity of the process towards the formation of the carbonyl derivative instead of the alcohol was enhanced by the addition of carboxylic acids. Furthermore, a practical iron-catalysed benzylic oxidation utilising *tert*-butyl hydroperoxide (TBHP) as the oxidant was developed.²⁷ In this case, the presence of inexpensive $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ facilitated the oxidation of a wide range of benzylic substrates to the corresponding carbonyl compounds. The addition of a ligand or another additive was unnecessary in this system (Scheme 7, eqn (13)).

Recently, White and Chen developed an elegant iron catalysis for the selective oxidation of aliphatic C–H bonds with H_2O_2 as the oxidant and acetic acid as an additive.²⁸ They demonstrated that the oxidation reaction of unactivated substrates to the corresponding hydroxylated compounds could be predicted even in complex molecules on the basis of the electronic and steric environment of the C–H bond. Thus, in most cases such hydroxylation reactions took place preferentially at the most electron-rich tertiary C–H bonds and, importantly, when such C–H bonds were part of a stereogenic centre, retention of configuration was always observed. Besides, it was found that carboxylate groups directed the C–H oxidation toward the formation of five-membered lactones. The authors proved the high value of this method by selectively introducing hydroxy functionalities at a late stage in the synthesis of natural products of high structural complexity. For example, compared to enzymatic conversions, their C–H oxidation protocol proved superior in the transformation of the antimalarial compound (+)-artemisinin to give (+)-10 β -hydroxyartemisinin.

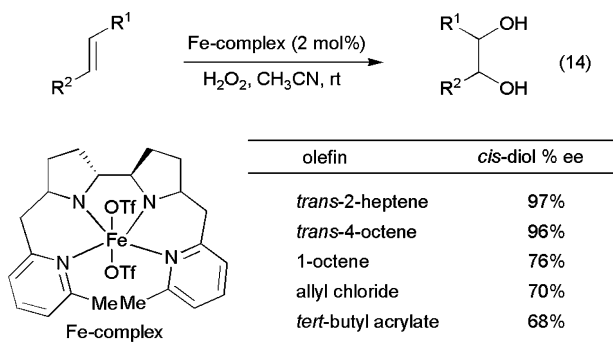
Alkene oxidations. In analogy to the peroxide reactions observed for several iron enzymes, a number of iron complexes

have been applied as catalysts in alkene oxidations.²⁹ In most detail, iron complexes bearing amine–pyridine–ligands such as TPA [tris(2-pyridylmethyl)amine] or BPMEN [*N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)-1,2-diaminoethane] have been investigated. Olefin *cis*-dihydroxylations and epoxidations are related processes that can be observed with similar iron–oxo species. Depending on the nature of the iron catalyst, the oxidant and the additive either pathway can be favoured.

High-valent iron–oxo compounds are generally proposed as the responsible oxidants for the oxygenation reaction. Along these lines, a strong emphasis has recently been put on the elucidation of the exact nature of the active oxidising species and the mechanistic understanding of the oxygen transfer from non-heme iron–oxo intermediates to alkenes. For example, Que and Comba investigated the mechanism of the H_2O_2 shunt olefin oxidation catalysed by bispidine–iron(II) complexes.^{30,31} As for the tetradentate TPA and BPMEN based catalysts,²⁹ low-spin $[(\text{L})\text{Fe}^{\text{III}}\text{OOH}]$ and intermediate-spin $[(\text{L})\text{Fe}^{\text{IV}}=\text{O}]$ complexes have been suggested as relevant intermediates in the catalytic process. On the other hand, DFT studies and experimental data for certain pentadentate bispidine–iron systems indicated the presence of other active species.³¹ In those cases, previously non-considered intermediate-spin $[(\text{L})\text{Fe}^{\text{IV}}(\text{OH})_2]$ and high-spin $[(\text{L})\text{Fe}^{\text{IV}}=\text{O}(\text{OH}_2)]$ iron oxidants could be involved as catalytically active intermediates.

As mentioned before, additives such as water or acetic acid can change the mechanism and thereby alter the catalytic activity of the iron complexes. For example, in the presence of acetic acid, the *cis*-diol formation is commonly suppressed and the selectivity towards epoxidation improved. The almost unexplored mechanism of the iron-catalysed olefin epoxidation with H_2O_2 –acetic acid was studied by Mas-Ballesté and Que.³² The results of experimental and theoretical studies on TPA and BPMEN based iron complexes suggested that the most likely epoxidating agents were high-valent acetic oxo–iron species $[(\text{L})\text{Fe}^{\text{V}}=\text{O}(\text{OAc})]^{2+}$, generated from the O–O bond heterolysis of the corresponding hydroperoxo intermediates $[(\text{L})\text{Fe}^{\text{III}}(\text{OOH})(\text{AcOH})]^{2+}$. Additionally, it was found that the topology of the ligand surrounding the iron centre played an important role in the selectivity of the oxidation reaction.³³ Although at the present time no clear explanation for this effect can be given it is evident that the *trans* or *cis* geometry adopted by the iron complex dramatically influences its catalytic activity.

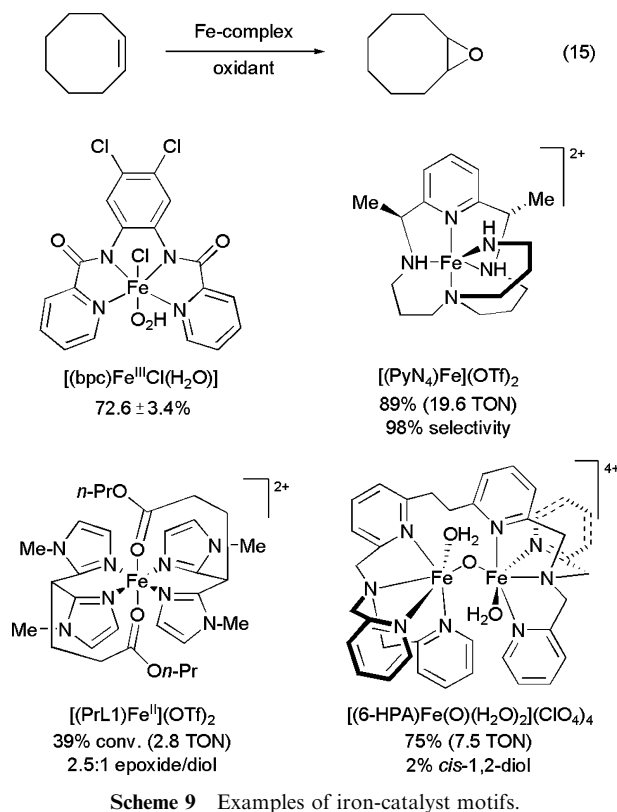
Que and co-workers also synthesised a bio-inspired non-heme iron-catalyst for the selective *cis*-dihydroxylation of olefins with H_2O_2 as the oxidant.³⁴ An asymmetric version was more recently introduced providing diols with high enantioselectivities (up to 97% ee).³⁵ After comparing the activity of several iron complexes it was found that $[\text{Fe}^{\text{II}}(6\text{-Me}_2\text{-BPBP})(\text{OTf})_2]$ (BPBP = bis(2-pyridylmethyl)-(*R,R*)-2,2',2''-bipyrrolidine) was highly selective towards *cis*-diol formation (Scheme 8, eqn (14)) and that furthermore its enantioselectivity compared well to the one obtained in Sharpless' osmium-based asymmetric dihydroxylations. Electron-rich *trans*-disubstituted olefins (*trans*-2-heptene and *trans*-4-octene) and several terminal alkenes (1-octene, allyl chloride and *tert*-butyl acrylate) provided the highest enantioselectivities with ee values ranging from 68 to 97%.



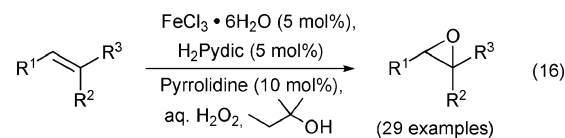
Scheme 8 Iron-catalysed *cis*-dihydroxylations.

The typical test epoxidation reaction consists of the oxidation of cyclooctene, as the corresponding epoxide is highly stable (Scheme 9, eqn (15)). In addition to the aforementioned iron-complexes with the TPA and the BPMEN ligand backbones, new classes of functional models for non-heme iron-based oxygenases have been reported lately. Some recent examples are shown in Scheme 9. These include iron complexes of novel tetra-³⁶ or pentadentate amino-pyridine ligands,³⁷ *N,N,O*-ligands,³⁸ and (μ -oxo)diiron complexes.³⁹

As a response to the need for basic and more practical systems for olefin epoxidations, Beller *et al.* have reported a simple procedure using commercially available, cheap and easy to handle $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as the catalyst.⁴⁰ A combination of 2,6-pyridine dicarboxylic acid (H_2Pydic) as a ligand and pyrrolidine as the base in an alcoholic media was found to be highly effective for the epoxidation of *trans*-stilbene. Amines such as triethylamine, benzylamine or imidazole were also applicable, and the optimised protocol allowed efficient and



Scheme 9 Examples of iron-catalyst motifs.



$R^1 = \text{Ar}; R^2, R^3 = \text{H, Ar, Alk}$ up to 97% ($\leq 99\%$ selectivity)
 $R^1, R^2, R^3 = \text{H, Alk}$ up to 36% ($\leq 75\%$ selectivity)

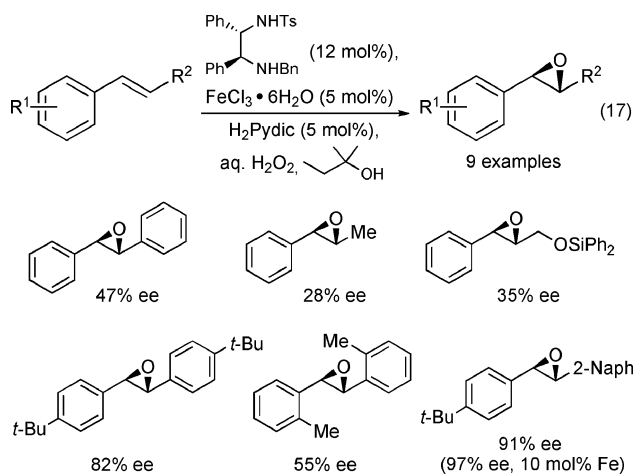
Scheme 10 FeCl_3 - H_2Pydic -pyrrolidine system.

highly selective oxidations of several substituted alkenes. Excellent reactivities and selectivities were achieved in conversions of aromatic olefins and moderate reactivity resulted from reactions with aliphatic substrates (Scheme 10, eqn (16)).

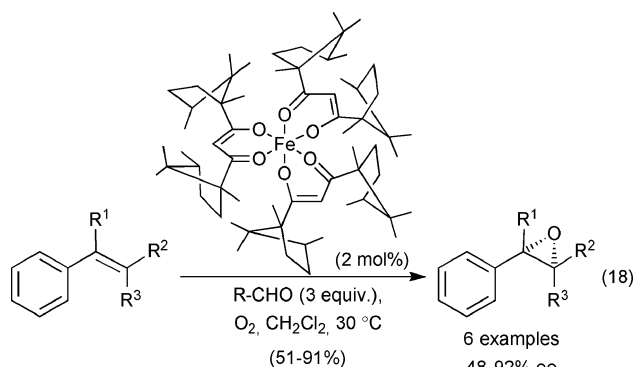
The same authors have recently described iron-catalysed asymmetric epoxidations of aromatic alkenes employing non-porphyrin ligands.⁴¹ In this study, enantiopure monosulfonyldiamine ligands derived from C_2 -symmetric 1,2-diamines were tested. The best results were obtained with (*S,S*)-*N*-tosyl-*N'*-benzyl-1,2-diphenylethylenediamine as the ligand. Thus, a variety of substituted *trans*-styrenes were successfully epoxidised in good yields. The enantioselectivities varied from low to excellent depending on the substrate (up to 97% ee, Scheme 11, eqn (17)).

A prior enantioselective iron-catalysed epoxidation was described by Cheng *et al.* (Scheme 12, eqn (18)).⁴² They oxidised styrene derivatives under aerobic conditions in the presence of $\text{Fe}(\text{dcm})_3$, a chiral (β -diketone)iron(III)-complex derived from *D*-camphor. Moderate to good enantioselectivities (up to 92% ee) were achieved, however, the addition of a sacrificial aldehyde as reducing agent was required to minimise the cleavage of the double bond in the styrene moiety.

Rearrangements. Iron salts have also found applications in rearrangement reactions such as the Ferrier rearrangement, which consists of the allylic rearrangement of glycol esters in the presence of alcohols leading to 2,3-unsaturated glycosides. Zhang and co-workers observed that ferric sulfate hydrate catalysed the Ferrier rearrangement of both peracetyl and perbenzyl glucals to afford regioselectively 2,3-unsaturated-*O*-glucosides (Scheme 13, eqn (19)). No addition products were detected under such conditions.⁴³ Additionally, they



Scheme 11 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ -catalysed asymmetric epoxidations.



Scheme 12 Enantioselective epoxidation with $\text{Fe}(\text{dcm})_3$.

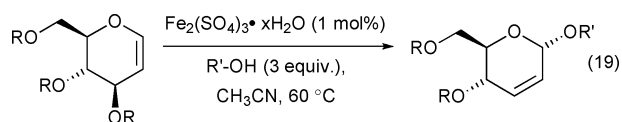
proved that under microwave irradiation similar results were obtained but in comparatively shorter reaction times.

2.3. Carbon–sulfur bond formation

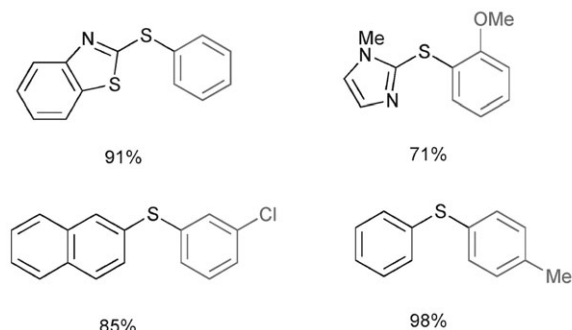
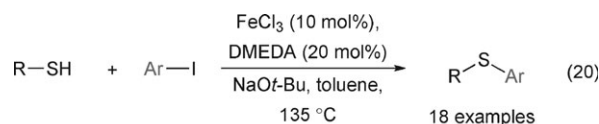
S-Arylations. Whereas numerous efficient C–N and C–O bond forming processes have been established so far, the C–S bond formation remains comparatively less studied. Nevertheless, given the prevalence of C–S bonds in a wide range of pharmaceutically active compounds and polymeric materials, it is essential to design novel cost-efficient and improved procedures for such synthetic purposes. In this respect, the lack of an iron-catalysed C–S cross-coupling protocol between thiol derivatives and aryl halides, commonly named as *S*-arylations, challenged the application of the aforementioned iron catalysts previously used in *N*- and *O*-arylations to such demanding transformations.

Despite the fact that thiols are generally stronger nucleophiles than alcohols and amines, their sensitivity towards oxidation resulting in the undesired formation of disulfides (oxidative S–S coupling) makes aryl–sulfur bond forming processes more difficult. However, it was found that the combination of FeCl_3 and DMEDA was particularly effective for the *S*-arylation of numerous thiols with aryl iodides as the electrophilic counterparts.⁴⁴ Indeed, test experiments in the absence of the diamine ligand, which provided the undesired disulfide as the major product, revealed that the chemoselectivity towards the *S*-arylation reaction was completely controlled by the addition of the diamine. Hence, this iron catalyst allowed the selective coupling of several aromatic and heterocyclic thiols with differently substituted aryl iodides in good to excellent yields (Scheme 14, eqn (20)).

Michael additions. Another important type of C–S bond forming process to which iron catalysis has been applied is the Michael addition reaction, which consists of the conjugate addition of a nucleophile to an acceptor olefin activated by an electron-withdrawing group. Although iron-catalysed versions of this transformation to form C–C single bonds has been widely explored, their extension to C–S bond formation



Scheme 13 Iron-catalysed Ferrier rearrangements.

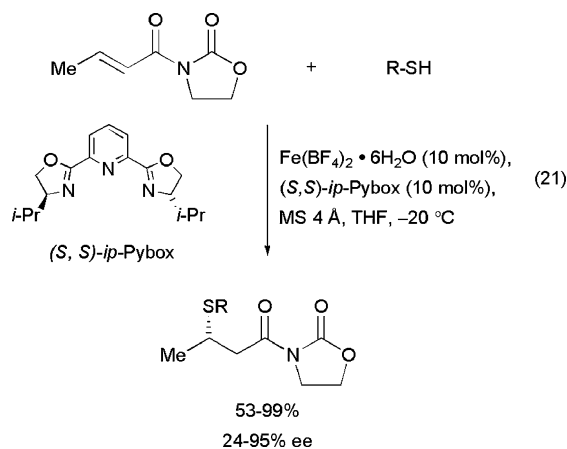


Scheme 14 Iron-catalysed *S*-arylations.

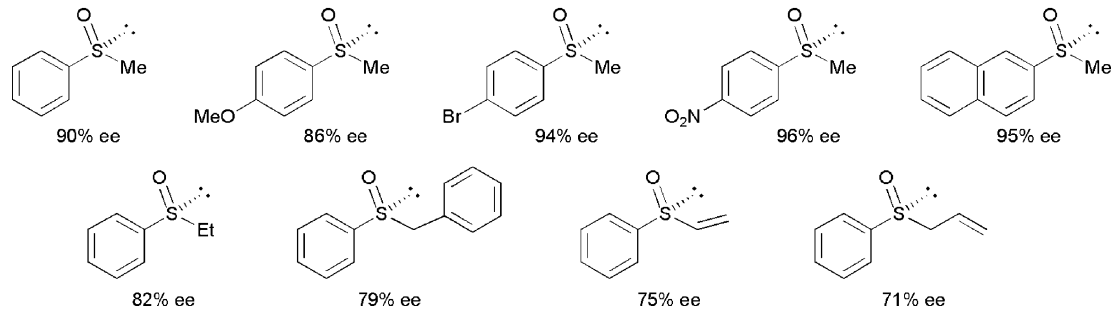
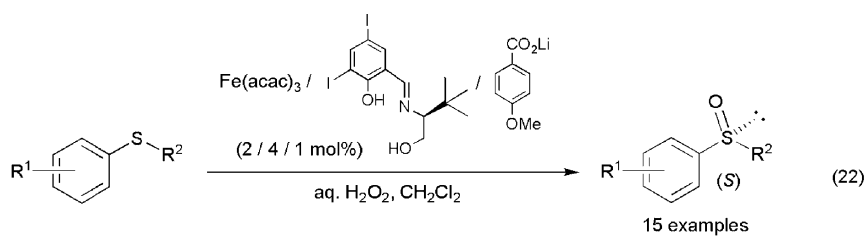
remained unknown until 2006 when the first iron-catalysed 1,4-additions of thiols to α,β -unsaturated ketones and esters were published.⁴⁵ Yao and co-workers found that numerous cyclic and acyclic enones and esters underwent 1,4-addition of aromatic and aliphatic thiols to give the corresponding Michael adducts in high yields. Furthermore, they observed that, in comparison with conventional methods involving other metals, the use of anhydrous FeCl_3 enhanced reaction rates, yields and selectivity towards the 1,4-addition reaction. More recently, the first enantioselective Michael additions of thiols to α,β -unsaturated amides catalysed by a combination of iron salts and bis(oxazoline)-based chiral ligands were developed.⁴⁶ Kawatsura, Itoh *et al.* discovered that the iron catalyst prepared from $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ and a pybox-type ligand efficiently assisted the asymmetric Michael addition of thiophenols to (*E*)-3-crotonoyloxazolidin-2-one to afford the corresponding addition products in high yields and enantioselectivities (up to a 95% ee; Scheme 15, eqn (21)).

3. Heteroatom–heteroatom bond formation

Although less studied than the previous carbon–heteroatom bond-forming processes, iron-catalysed reactions have been also used to create heteroatom–heteroatom bonds. Among



Scheme 15 Iron-catalysed asymmetric Michael addition.



Scheme 16 Sulfide oxidation with an $\text{Fe}(\text{acac})_3$ -Schiff base system.

them, formation of sulfur–oxygen or sulfur–nitrogen bonds has mainly been studied.

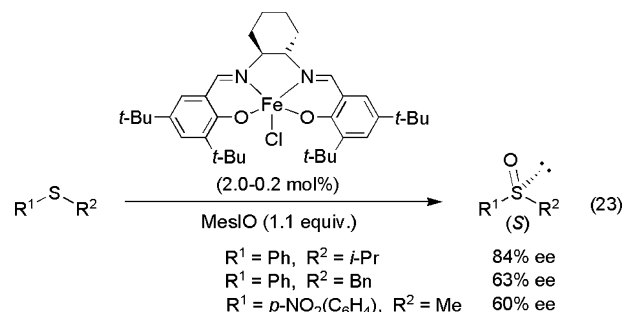
3.1. Sulfur–oxygen bond formation

The selective oxidation of sulfides to sulfoxides with various metal-catalysts has been extensively explored. Of special interest are asymmetric versions of this transformation. In this sense, effective and enantioselective iron-catalysed oxidations of sulfides to sulfoxides have been reported lately, offering alternatives to existing methods.

A significant progress in this field was achieved by Legros and Bolm a few years ago.⁴⁷ They reported the first highly enantioselective iron-catalysed asymmetric sulfide oxidation. The reaction involved very simple reaction conditions using iron(III) acetylacetonate [$\text{Fe}(\text{acac})_3$] as a pre-catalyst in combination with a Schiff-base type ligand. In addition, harmless and inexpensive aqueous hydrogen peroxide was used as the oxidant (Scheme 16, eqn (22)). Shortly after, studies on the kinetics and the effect of different carboxylic acids and carboxylate salts as additives on the reactivity and enantioselectivity were carried out.⁴⁸

The presence of 1 mol% of lithium 4-methoxybenzoate improved significantly the effectiveness of the process, and optically active aryl alkyl sulfoxides were obtained with remarkable enantioselectivities and in moderate to good yields. The best results were achieved in the oxidation of methyl aryl sulfides (up to 96% ee). Besides, good enantiomeric excesses were also reached with more challenging substrates having ethyl, benzyl, vinyl or allyl groups (71–82% ee). The positive non-linear relationship between the enantiomeric excess of the product and the catalyst was interpreted as possible participation of a bridging monocarboxylate diiron species.

Bryliakov and Talsi reported on the use of chiral [iron(salen)Cl] catalysts for asymmetric sulfide oxidation using iodosylarenes (ArIO) as terminal oxidants.⁴⁹ The authors showed that the nature of the iodosylarenes employed clearly influenced the chemo- and enantioselectivities of this process. Thus, good selectivities in the formation of sulfoxides *vs.*



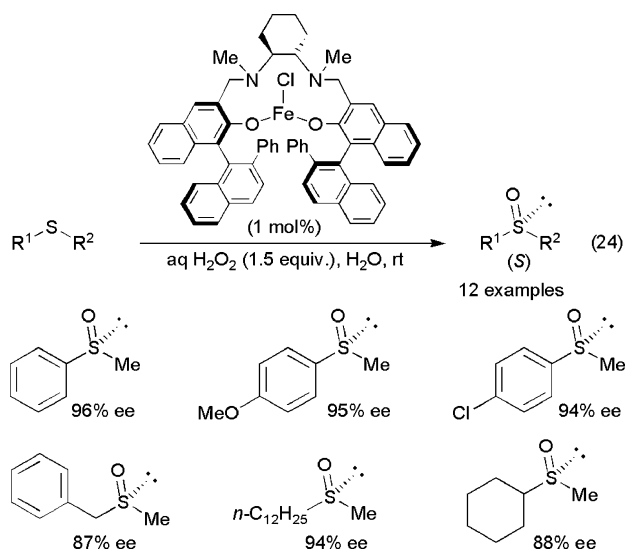
Scheme 17 $\text{Fe}(\text{salen})\text{Cl}$ -catalysed oxidation of thioethers.

sulfones were obtained, and moderate to good enantiomeric excesses were achieved with MesIO as the oxidant (60–84% ee, Scheme 17, eqn (23)). Additionally, they proposed the involvement of an $[\text{Fe}^{\text{III}}(\text{ArIO})(\text{salen})]$ complex, which could be detected by NMR spectroscopy.

More recently, Katsuki and Egami have developed a highly efficient $\text{Fe}(\text{salan})$ -catalysed sulfide oxidation in water using H_2O_2 as the oxidant (Scheme 18, eqn (24)).⁵⁰ The reaction proceeded in ambient air and at room temperature in the presence of a low catalyst loading (1 mol%). High yields and enantioselectivities were achieved for both alkyl–aryl and alkyl–alkyl sulfoxides (81–96% ee).

3.2. Sulfur–nitrogen bond formation

Iron-catalysed nitrene transfers to sulfides and sulfoxides to obtain sulfilimines and sulfoximines, respectively, have only attracted attention in the past few years. Recently it was discovered that inexpensive and easy to handle $\text{Fe}(\text{acac})_3$ was capable of catalysing the imination of sulfur compounds using sulfonyl amides in combination with iodosylbenzene (PhIO) as a terminal oxidant.⁵¹ Use of 5 mol% of the iron catalyst permitted the successful imination of a variety of alkyl and aryl sulfides and sulfoxides, leading to the corresponding sulfilimines and sulfoximines in good yields. The best results were obtained with *p*-nitrobenzene sulfonylamide (NsNH_2) as

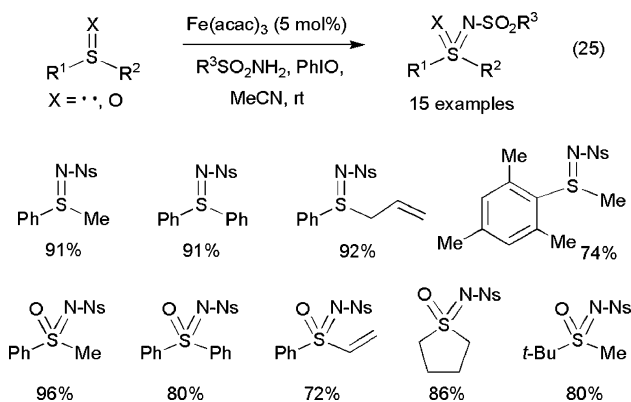


Scheme 18 Sulfide oxidation in water with an Fe(salan)Cl catalyst.

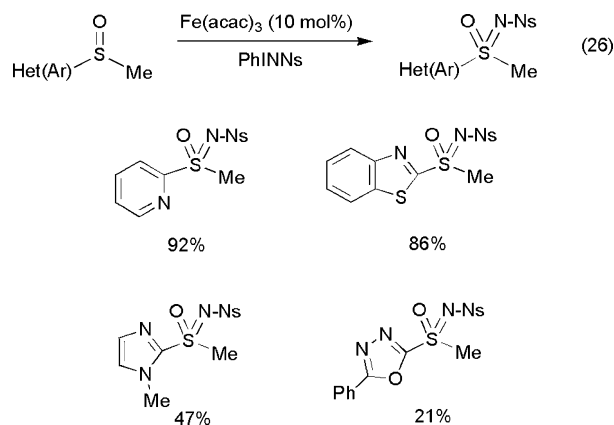
the nitrogen source (Scheme 19, eqn (25)). Competitive studies showed that sulfides were more readily iminated than sulfoxides.⁵²

The reaction proceeded stereospecifically with retention of configuration at sulfur, and it thereby constituted an alternative access to enantiopure sulfoximines from the corresponding chiral sulfoxides. Furthermore it is noteworthy that the deprotection of the *N*-nosyl products led to synthetically more valuable *NH*-sulfoximines.

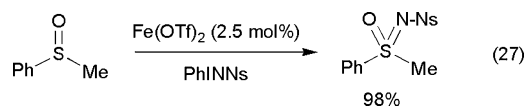
In analogy with the corresponding well-known high-valent iron–oxo complexes [(L)Fe=O], an iron–nitrene complex [(L)Fe=NR] has been suggested as a reactive intermediate. However, to date no evidence on the nature of the active catalyst has been obtained. Regarding possible active high-valent iron species participating in such reaction, Que *et al.* has recently reported the characterization of a non-heme tosyl-imido–iron(IV) complex based on an amino–pyridine ligand.⁵³ Despite the good results obtained with aryl and alkyl substrates employing Fe(acac)₃ as the catalyst, the intricate imination of heterocyclic sulfoxides has remained a challenge. In comparison to other metal-based catalytic systems, the iron catalyst showed promising reactivities with substrates containing heteroatoms using pre-formed iminoiodinane PhINNs as



Scheme 19 Fe(acac)₃-catalysed sulfur iminations.



Scheme 20 Nitrene transfer to heterocyclic sulfoxides.



Scheme 21 Fe(OTf)₂ as catalyst for the imination of sulfoxides.

the nitrene precursor.⁵² However, the success is still limited, and various heteroaromatic sulfoxides can not yet be efficiently iminated under these conditions (Scheme 20, eqn (26)).

To overcome this restriction, new iron catalysts have been explored. In preliminary studies, Fe(OTf)₂ showed outstanding reactivity towards the imination of phenyl methyl sulfoxide.¹⁷ Only 2.5 mol% of this iron species was needed to catalyse this transformation in a short reaction time and excellent yield (1 h, 98% yield; Scheme 21, eqn (27)). The unexpected high reactivity of this iron-based catalytic system has encouraged further studies on its applicability in the imination of more challenging substrates.

Conclusions

Due to their ready availability, environmental friendliness and low price along with their exceptional reactivity, iron catalysts have evolved in recent years as a truly valuable and advantageous tool to effect a wide range of important synthetic processes. In this review, we have compiled a selection of the latest transformations catalysed by this valuable metal to assemble carbon–heteroatom and heteroatom–heteroatom linkages, which are present in numerous biologically active molecules and compounds of industrial significance. We are convinced that some of the iron-catalysed methodologies presented here will emerge as reliable and competitive processes to other existing transition metal-catalysed methods in the next few years. Besides, continued growth and promising advances in this field are expected.

Acknowledgements

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