

Iron-Catalyzed Reactions in Organic Synthesis

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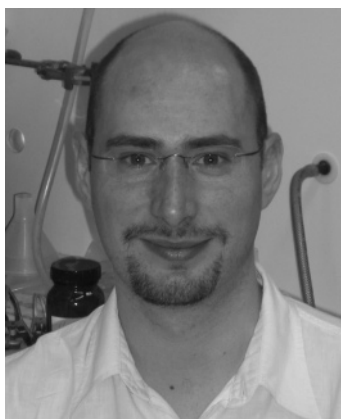
1. Introduction

Metal complexes are essential instruments in the toolbox of organic chemists. The current requirements for clean, fast, efficient, and selective processes have increased the demand for such metal-based reaction promoters, especially the ones that can be applied in catalytic amounts and/or that are recyclable. However, many catalysts are derived from heavy or rare metals and their toxicity and prohibitive prices constitute severe drawbacks for large-scale applications. In contrast, iron is one of the most abundant metals on earth, and consequently one of the most inexpensive and environmentally friendly ones.¹ Moreover, many iron salts and complexes are commercially available,² or described in the literature.³ Despite its advantages, it is surprising that, until recently, iron was relatively underrepresented in the field of catalysis compared to other transition metals.⁴ The most famous application was the Reppe synthesis and related processes.⁵ However, the last few years have seen a rise of its use, and some very effi-

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Carsten Bolm was born in 1960. He studied chemistry at the TU Braunschweig (Germany) and at the University of Wisconsin, Madison (USA). In 1987, he obtained his doctoral work performed under the supervision of Professor Reetz in Marburg (Germany). After postdoctoral training with Professor Sharpless at MIT, Cambridge (USA), Carsten Bolm worked with Professor Giese at the University of Basel (Switzerland) to obtain his habilitation. In 1993, he became Professor of Organic Chemistry at the University of Marburg (Germany), and since 1996 he is full professor for Organic Chemistry at the RWTH Aachen (Germany). At the universities in Madison, Wisconsin (USA), Paris (France), Florence (Italy), Milan (Italy), and Namur (Belgium) he held visiting professorships, and his awards include the Heinz-Maier-Leibnitz prize, the ADUC-Jahrespreis for habilitands, the annual prize for Chemistry of the Akademie der Wissenschaften zu Göttingen, the Otto-Klung prize, the Otto-Bayer award, and a fellowship of the Japan Society for the Promotion of Science.



Julien Legros was born in 1974 near Paris, France. He studied at the Universities of Paris XII-Créteil and Paris XI-Orsay and obtained his MSc degree in 1999. He then did his doctoral studies in the field of organofluorine chemistry under the guidance of Drs. Bégue and Bonnet-Delpon at the Faculty of Pharmacy of Paris XI in Châtenay-Malabry, and received his Ph.D. degree in 2002. Subsequently, he joined Professor Bolm's group at the RWTH-Aachen (Germany) as an Alexander von Humboldt postdoctoral fellow, working on iron-catalyzed oxidations. He is currently holding a permanent CNRS researcher position in the group of Dr. Bonnet-Delpon.

cient processes able to compete with other metal-catalyzed ones have emerged, also in the field of asymmetric catalysis.⁶ This development encouraged us to summarize the use of iron catalysts in organic synthesis in a general review, which includes reactions in which the metal is directly involved in the mechanism (thereby excluding ferrocenes,⁷ for example). Iron-catalyzed systems for C–H oxidation (Gif⁸ and Fenton chemistry,⁹ nonheme mimic systems¹⁰), olefin epoxidation,¹⁰ and the chemistry of Fe-porphyrins,¹¹ have already been summarized in various reports and



Jacques Le Paih was born in 1972 in Vannes (France). He graduated from the Université de Rennes in 1996. He completed his Ph.D. in 2000 under the supervision of Professor Dixneuf at the Université de Rennes. His Ph.D. thesis was entitled "New Methods for the Formation of Carbon–Carbon Bonds via Ruthenium Catalysis". He was then awarded an Alexander von Humboldt Fellowship in 2001 and joined the research group of Professor Bolm at the RWTH-Aachen (Germany). His research work centered on catalytic asymmetric oxidation processes. Recently, he moved to Bristol (England) as an EPSRC Research assistant in the group of Professor Davis working on supramolecular electroneutral anionophores based on cholic acid for anion recognition.



Lorenzo Zani was born in Florence, Italy, in 1977. He studied chemistry at the University of Florence, where he earned his "Laurea in Chimica" in 2002, with a thesis on the elaboration of aziridines by means of superbasic reagents, under the supervision of Dr. Mordini. In 2003, he joined the research group of Professor Bolm, where he is currently carrying out his Ph.D. studies working on metal-catalyzed asymmetric C–C bond forming reactions.

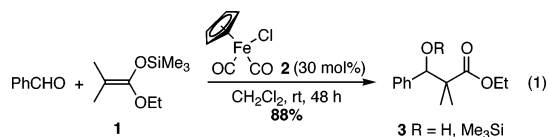
are regarded as out of the scope of this review. Relevant papers that have appeared by spring 2004 are compiled on the basis of reaction types.

2. Addition Reactions

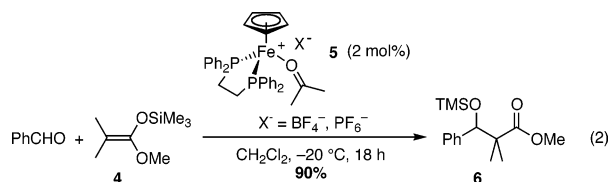
2.1. Aldol Reactions and Related Processes

The Mukaiyama-aldol reaction is one of the most widely employed methodologies to form carbon–carbon single bonds;¹² the result of this reaction is an α -hydroxy carbonyl compound, which can be either obtained as silylenol ether or free alcohol. Several catalytic systems are available,¹³ some of which utilize iron compounds as catalysts. In 1989, Colombo et al. reported that dicarbonyl cyclopenta-

dienyl iron halides were effective catalysts for the addition of ketene acetals to aldehydes (eq 1).¹⁴

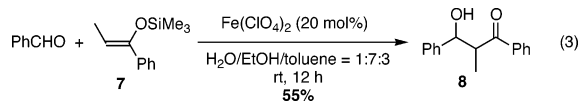


Three years later a similar reaction was performed using cationic iron complexes bearing a cyclopentadienyl and a diphosphine ligand (eq 2).¹⁵



Interestingly, a corresponding homobinuclear iron complex exhibited a higher activity, allowing the realization of the same transformation in 1 h at -78 °C without any loss in yield. The authors propose in this case a double coordination of the aldehyde by the two iron atoms of the catalyst, leading to the enhanced reactivity shown by the carbonyl compound.¹⁵

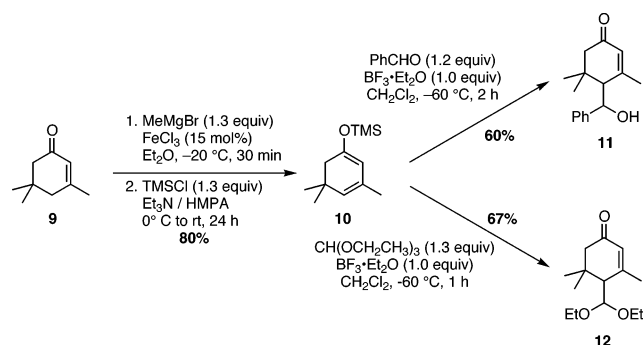
More recently, Mukaiyama-aldol reactions have been performed in aqueous medium,¹⁶ employing several Lewis acids as catalysts (eq 3).¹⁷ Although the best results were obtained with lanthanide triflates, iron salts also demonstrated a considerable activity. The yield of the aldol adduct was however strongly affected by various parameters such as the oxidation state of the metal, the nature of the anion, and the cosolvent used.



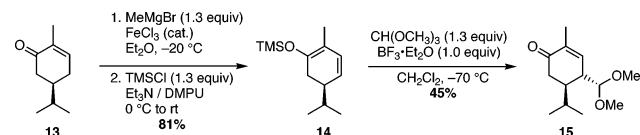
Very recent studies demonstrated that the efficiency of this methodology could be greatly enhanced if the reaction was carried out in the presence of a catalytic amount of a surfactant (normally sodium dodecyl sulfate or similar compounds). Thus, for the reaction shown in eq 3 aldol product **8** was obtained with up to 90% yield and a remarkable 90/10 *syn/anti* diastereoselectivity, when 10% of FeCl₃ (which previously had been regarded as a water-incompatible Lewis acid) was used as a catalyst in pure water.¹⁸

The aldol reaction can be extended in vinylogous terms,¹⁹ when a conjugated silyldienol ether is used as the nucleophile. Such species are usually prepared from α,β -unsaturated ketones or esters, in some cases by means of an iron-catalyzed process. In an early report,²⁰ Kharasch and Tawney observed that the reaction of the α,β -unsaturated ketone isophorone (**9**) with methylmagnesium bromide in the presence of a catalytic (20 mol %) amount of FeCl₃ led to a selective deprotonation of the starting material. Trapping of the intermediate magnesium enolate with trimethylsilyl chloride gave conjugated trimethylsilyl enoether **10**, which was then used as

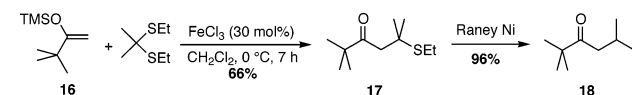
Scheme 1



Scheme 2



Scheme 3



nucleophile in the reaction with aldehydes and orthoformates (Scheme 1).²¹

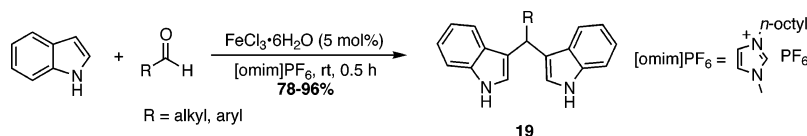
The resulting products were then used for the syntheses of some megastigmane derivatives. The same procedure was applied in the synthesis of sarcodictyins and eleutherobin by Gennari and co-workers, who utilized a (-)-carvone derivative as starting material (Scheme 2).²² It should be noted that in this case the reaction proceeded with complete stereoselectivity, affording only the product resulting from the formylation of the less hindered side of the intermediate dienoxysilane **14**.

A transformation conceptually related to the Mukaiyama-aldol reaction is the α -alkylation of carbonyl compounds.²³ The only iron-catalyzed process reported so far concerns the reaction of silyl enoether **16** with a dithioacetal (Scheme 3). One of the thioethyl groups is substituted, and the other can be subsequently removed by reduction, thus affording alkylation product **18**.²⁴

Another example of an iron-catalyzed addition of a nucleophile to a carbonyl compound was recently described by Loh and co-workers.²⁵ They found that in ionic liquids iron trichloride hexahydrated was a very effective catalyst for the double addition of indole to aldehydes yielding bis(indolyl)methanes **19** in high yields (Scheme 4).

The only other Lewis acid that furnishes results comparable to the ones obtained with FeCl₃·6H₂O is In(OTf)₃, but because of its lower cost the iron salt is clearly preferable. Moreover, the iron catalyst was immobilized in the ionic liquid, and since the workup of the reaction consisted of a simple extraction of the product with diethyl ether, it could be reused several times without loss of activity (although longer reaction times had to be accepted). In contrast, the activity of the indium salt decreased dramatically after only two catalytic cycles.

Scheme 4

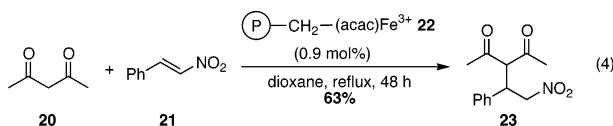


2.2. Michael Additions and Other Conjugate Addition Reactions

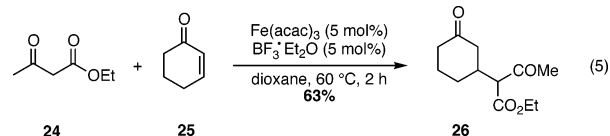
The Michael reaction is the conjugate addition of an enolate to an acceptor olefin activated by an electron-withdrawing group, such as an enone, which, in most cases, results in the formation of a 1,5-dioxo constituted product. The reaction has been traditionally performed using catalytic amounts of a Brønsted base,²⁶ but more recently acid-²⁷ and metal-catalyzed²⁸ versions of the Michael addition have been reported. The use of these conditions allowed avoiding the usual drawbacks of the base-catalyzed process, in particular, side reactions such as aldol cyclizations or retro-aldol decompositions.

Among the various metal compounds used to catalyze this reaction, iron salts, and in particular ferric chloride hexahydrate, were clearly the catalysts of choice.²⁹ Nevertheless, other systems have also been reported, and they will be discussed here as well.

In 1982, Fei and Chan reported that the addition of β -diketones to β -nitrostyrenes was catalyzed by polymer-anchored metal acetylacetonates,³⁰ including iron ones (eq 4). A very low catalyst loading could be used, but only moderate yields of the product were obtained.

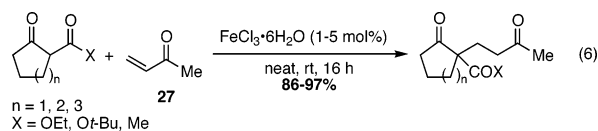


Iron(III) acetylacetonate was successively used as homogeneous catalyst for the addition of ethyl acetoacetate to cyclohexenone (eq 5).³¹ The reaction was found to proceed only in the presence of an equimolar amount (with respect to iron) of a Lewis acid, and also in this case the yield of the product did not exceed a moderate value.



Another example of such a dual catalysis was reported later by Laszlo et al., who used a supported metal species (typically, nickel dibromide on K10 montmorillonite) in the presence of anhydrous iron trichloride to catalyze the addition of β -dicarbonyls to various acceptors.³² Very good yields were achieved employing mild reaction conditions. It should be noted that in this case FeCl_3 was suggested to act as a Lewis acid (activation of the acceptor), while the donor was proposed to coordinate to the supported nickel compound.

Since its introduction in 1997, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ has been considered as the best catalyst for Michael reactions. Indeed, excellent results have been obtained for the addition of a number of cyclic and acyclic β -dicarbonyls to various acceptors even with very low catalyst loadings and under mild reaction conditions (eq 6).³³



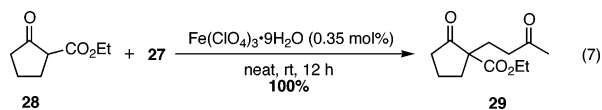
The main limitation of the system relates to the stereochemistry of the acceptors. The reactions, in fact, are not effective when 1,2-disubstituted (*Z*)-enones are used as substrates. With (*E*)-substituted enones, the reactions proceed smoothly affording mixtures of diastereomers, whose composition is normally similar to the one obtained under base-catalyzed conditions. Notably, for some substrates iron(III) catalysis is capable of producing mixtures of kinetic diastereomers even in cases in which base catalysis leads to a thermodynamic equilibrium mixture.

Very recently, an improvement of this methodology based on the use of a solid-supported iron(III) catalyst appeared in the literature.³⁴ By using as small as 1 mol % of an iron(III)-exchanged fluorotetrasilicic mica a clean reaction between various β -ketoesters and methylvinyl ketone (MVK, **27**) was achieved under mild reaction conditions. The yields were practically quantitative, and the catalyst was reusable at least four times without any loss of activity. Kinetic studies demonstrated that this supported iron species was even more active than the homogeneous catalyst $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$.

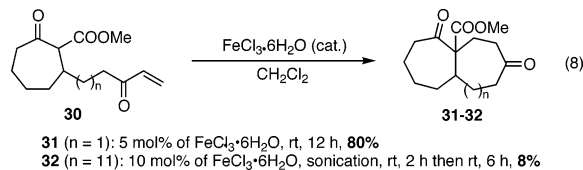
The iron-catalyzed Michael addition of acetylacetonate (**20**) to MVK (**27**) has also been performed in ionic liquids.³⁵ While after a first series of experiments it seemed that $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ was completely unable to promote the reaction in this type of medium,^{35a} in contrast to other metal salts, a reconsideration of the results led to the conclusion that the cause of the observed low activity was the presence of traces of halides in the solvent. When the reaction was repeated using a carefully dehalogenated ionic liquid as solvent, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ was found to be a remarkably active catalyst, affording the product with turnover frequencies up to 63 h^{-1} .^{35b}

The iron(III)-catalyzed Michael reaction of β -oxo esters with MVK (**27**) has also been the subject of computational studies.³⁶ The calculations suggested an acceleration of the reaction in the absence of an anionic spectator ligand such as chloride. From this result, an optimized protocol for the iron catalysis based on iron(III) perchlorate as the catalyst was derived. As a consequence, the amount of the metal

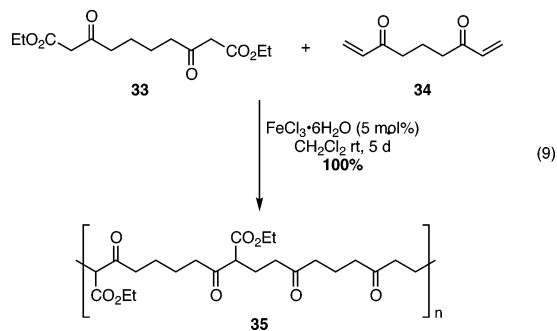
could significantly be reduced without affecting the yield (eq 7).



The use of an iron catalyst also allows the realization of the Michael addition in an intramolecular fashion, providing access to medium-sized rings.^{37,38} The reaction is stereoselective, furnishing only the *trans*-fused bicyclic product. Attempts to utilize this approach for the synthesis of macrocycles resulted in unsatisfactory yields (eq 8).



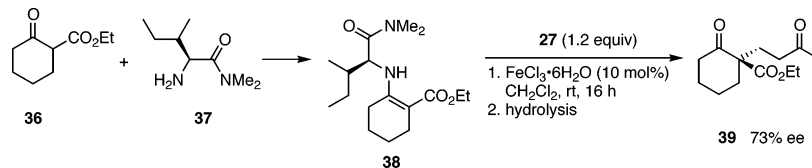
Employing bis-donor **33** and bis-acceptor **34**, a protocol for a stepwise polymerization based on successive Michael reactions has been developed. This process had no precedent in the literature and was made possible only by iron catalysis, thanks to the suppression of other possible side reactions (which occur in the base-catalyzed reaction) and the quantitative conversion of the starting materials (eq 9).³⁹ According to molecular mass measurements performed by GPC, the oligomeric product contained an average of 24 monomeric units (*n* = 12 in eq 9).



Recently, it has been reported that enolato iron(II) complexes derived from oxidative addition of ethyl cyanoacetate to [Fe(N₂)(depe)₂] (depe = 1,2-bis-(diethylphosphino)ethane) are capable of smoothly catalyzing a double Michael addition. Treatment of ethyl cyanoacetate with 2 equiv of acrylonitrile in the presence of 1 mol % of the complex gave the corresponding ethyl 2,2-di(cyanoethyl)cianoacetate in 88% yield after stirring in THF at room temperature for 36 h.⁴⁰

Efforts to develop an enantioselective version of the iron-catalyzed Michael addition have especially been

Scheme 5



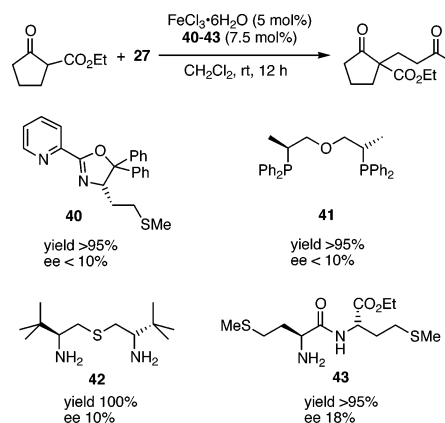
made by Christoffers, both by means of stoichiometric chiral auxiliaries and chiral ligands for asymmetric catalysis. Unfortunately, little success has been achieved in comparison with what could be realized with other metals.⁴¹

The reaction of MVK (**27**) with various chiral α -ketoesters (derived from enantiopure alcohols) afforded products in high yields, but with low levels of diastereoselectivity (up to 20% de).⁴² More fruitful was the use of α -amino acid amides **37** as chiral auxiliaries, which provided chiral enamines **38** from β -ketoesters. The iron-catalyzed reaction of **38** with MVK (**27**) followed by hydrolysis gave **39** with remarkable 73% ee (Scheme 5).⁴³

It should, however, also be noted that other metals furnished even better results. Thus, use of Cu(OAc)₂ under similar conditions gave **39** with 86% ee; after optimization, and using *L*-valine diethyl amide as the auxiliary, enantiomeric excesses up to 98% have been reached.

As mentioned above, catalytic asymmetric Michael additions have also been studied. Several molecules, such as pyridine-oxazoline **40**,⁴⁴ diphosphine **41**,⁴⁵ diaminothioether **42**,⁴⁶ and dipeptide **43**⁴⁷ have been applied as ligands, but the results in terms of enantioselectivity remained unsatisfactory (Scheme 6).

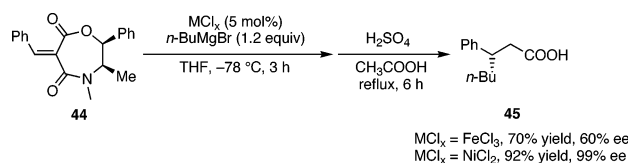
Scheme 6



In this case, the use of metals different than iron did not lead to any significant improvement, and the stereoselective construction of a quaternary stereocenter by means of asymmetric metal-catalyzed Michael reaction still remains an open task.⁴⁸

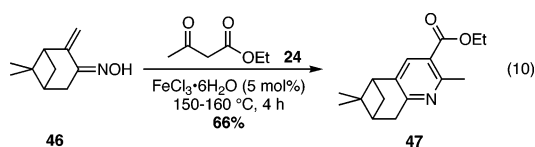
Iron catalysis has also been applied to different kinds of conjugate addition reactions, modifying both the acceptor and the donor. Mukaiyama et al. used FeCl₃ to catalyze the addition of Grignard reagents to optically active oxazepines **44**, to obtain enantiomerically enriched carboxylic acids.⁴⁹ Iron proved to be active in this transformation, but once again the results obtained with other metals (in particular,

Scheme 7



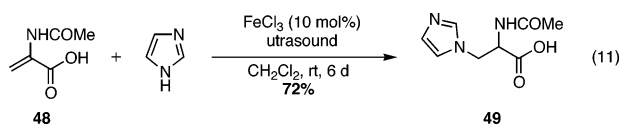
nickel) were superior both in terms of yield and selectivity (Scheme 7).

Recently, modified Michael reactions have been used for the synthesis of highly substituted pyridines, employing α,β -unsaturated oximes **46** as acceptors in the presence of ethyl acetoacetate (**24**) (eq 10).⁵⁰ Even under iron catalysis it was necessary to work at very high temperature to obtain the product. Nevertheless, the protocol is synthetically interesting due to its operational simplicity.



The mechanism of the pyridine ring formation is not yet clear, but a realistic hypothesis can be formulated as follows: after the conjugate addition of ethyl acetoacetate to the enone oxime, cyclization occurs, which is accompanied by elimination of a water molecule. The loss of a second molecule of water allows the system to become aromatic.

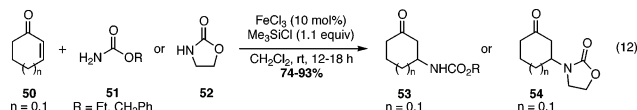
The use of donors with a nucleophilic nitrogen atom (aza-Michael reactions) has also been investigated, and it has been shown that iron(III) chloride is capable of catalyzing the addition of various secondary amines to α,β -unsaturated ketones and esters.⁵¹ Only 1,4-addition products are observed. A very similar protocol was recently applied in the conjugate addition of amines to α -acetamidoacrylic acid **48**, allowing the preparation of a number of β -dialkyl-amino- α -alanine derivatives.⁵² It is believed that in this case FeCl_3 acts as a Lewis acid, coordinating the acetamido group of **48** and consequently enhancing its reactivity as Michael acceptor (eq 11).



The aza-Michael reaction has also been performed under iron catalysis employing carbamates as nucleophiles.⁵³ Quite interestingly, among the various metal salts investigated, only FeCl_3 and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ proved to be active in the conjugate addition of ethyl carbamate to chalcone, the latter being more effective. In this case, the authors found that the addition of a stoichiometric quantity of Me_3SiCl , which is also a useful additive in the conjugate addition of organocopper reagents,⁵⁴ was necessary for the reaction to successfully proceed.

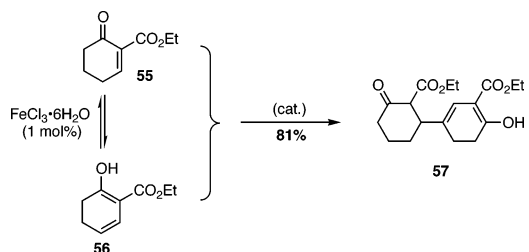
The best results have been achieved employing cyclic enones as substrates. At room temperature in

less than 24 h only the products arising from the 1,4-addition of the carbamates were obtained (eq 12).

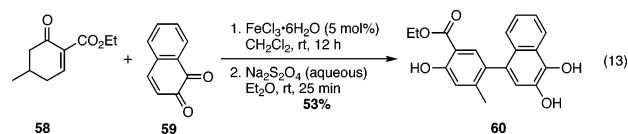


An iron(III) catalyst can be employed in a vinylogous variation of the Michael addition reaction.²⁹ This transformation was first reported in 1998 by Christoffers,⁵⁵ who observed the formation of a dimeric product, when a catalytic amount of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ was added to a solution of a cycloalkenone with an electron-withdrawing group in position 2 (Scheme 8).

Scheme 8



At a closer look, product **57** is (formally) derived from the addition of dienol **56** (as donor) to enone **55** (as acceptor). It should be pointed out, however, that the actual mechanism of the reaction is different and more complicated, involving probably a sequence of enone-dienol isomerization, Diels–Alder and retroaldol reactions. The reaction has been successively extended to various acceptors and donors⁵⁶ and was used for the synthesis of biaryl compounds **60** (eq 13).⁵⁷



Finally, an enantioselective conjugate radical addition catalyzed by $\text{Fe}(\text{NTf}_2)_2$ in the presence of chiral ligands, such as bisoxazolines (BOX) and pyridinyl bisoxazolines (PYBOX), has been reported in 2003.⁵⁸ When isopropyl iodide was used as radical precursor in combination with Bu_3SnH and $\text{Et}_3\text{B}/\text{O}_2$ as radical initiators, enantioselectivities of up to 98% ee were observed in the conjugate addition to *N*-cinnamoyl-2-oxazolidinone.

2.3. Allylations of Carbonyl Compounds and Acetals

The allylation of aldehydes by means of allylic metal reagents is a very important class of C–C bond forming reactions, since it gives rise to synthetically useful homoallylic alcohols **61**.⁵⁹ Generally, this reaction is catalyzed by Lewis acids. Very recently, iron species have been added to the relatively large number of catalysts known so far.

In 2002, Oriyama reported a very effective allylation of aldehydes with allyltrimethylsilane catalyzed by anhydrous iron(III) chloride (Table 1).⁶⁰ The reaction affords the homoallyl alcohols in high yields

Table 1. Iron(III)-Catalyzed Allylation of Aldehydes

$$\text{RCHO} + \text{CH}_2=\text{CH}-\text{SiMe}_3 \xrightarrow[2) \text{HCl 1N, 0.5 h}]{1) \text{FeCl}_3 (5 \text{ mol}\%), \text{MeNO}_2} \text{R}-\text{CH}(\text{OH})-\text{CH}_2-\text{CH}=\text{SiMe}_3$$
61

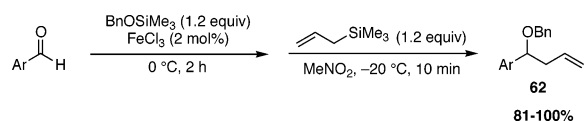
entry	RCHO	method ^d	yield (%) ^b	entry	RCHO	method ^d	yield (%) ^b
1		A	92	9		A	18
2		A	98	10		A	80
3		A	98	11		A	70
4		A	99	12		B	89
5		A	99	13		B	94
6 ^c		A	86	14		B	92
7		A	92	15 ^d		B	99
8		A	0	16		B	99

^a Method A: $-20\text{ }^\circ\text{C}$, 0.5 h. Method B: rt, 1 h. ^b Yields of purified products. ^c 2 mol % of FeCl_3 was used. ^d *syn/anti* = 1.8:1.

after short reaction times. Furthermore, it shows a remarkable generality, since both aromatic and aliphatic aldehydes can be converted, with a slight modification in the procedure.

As revealed by the data presented in Table 1, the only severe limitation of this method is the impossibility to convert electron-rich aromatic aldehydes, due to the formation of "over-allylated" products. Thus, *p*-tolualdehyde and *p*-anisaldehyde gave either a poor yield or no product at all (entries 8 and 9). This problem could be circumvented by applying the corresponding acetal as substrate instead of the aldehyde. Thus, in the presence of iron(III) the dimethyl acetal of *p*-anisaldehyde reacted smoothly with allyltrimethylsilane, affording the corresponding homoallyl methyl ether in high yield.⁶⁰

On the basis of these results and considering that it would be desirable to have a more reactive ether as the final product, an interesting one-pot synthesis of homoallyl benzyl ethers **62** starting from aldehydes was developed (Scheme 9).⁶¹

Scheme 9

A number of aromatic aldehydes could be transformed into the corresponding homoallyl benzyl ethers under very mild reaction conditions. Slightly harsher conditions allowed the conversion of aliphatic aldehydes.

Table 2. Iron-Catalyzed Electrochemical Coupling between Allyl Acetate and Carbonyl Compounds

$$\text{R}'-\text{C}(=\text{O})-\text{R}'' + \text{CH}_2=\text{CH}-\text{O}-\text{C}(=\text{O})-\text{R}''' \xrightarrow[2) \text{HCl 1M}]{1) \text{e}^-, \text{FeBr}_2 (10 \text{ mol}\%), \text{bipy} (0.5 \text{ equiv}), \text{DMF, Fe anode}} \text{R}'-\text{C}(\text{OH})(\text{R}'')-\text{CH}_2-\text{CH}(\text{R}''')-\text{CH}=\text{CH}_2$$
63

entry	substrate	n_{eq} of 63	product	yield (%) ^a
1		2		78
2		1.6		39
3		1.9		86
4		2.2		65
5		2.8		66
6		2.4		60
7		3		63
8 ^b		2		41
9 ^b		2		50

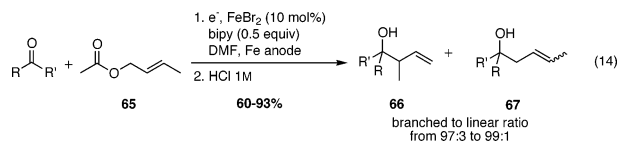
$\text{R} = \text{H, OAc}$

^a Yields based on the carbonyl compound. ^b First allyl acetate (**63**) was introduced, and RCHO was then added via syringe pump to minimize the direct reduction.

Other examples of iron-catalyzed allylation reactions of carbonyl compounds have recently been reported by Durandetti et al.⁶² In these reactions homoallyl alcohols **64** are prepared from aldehydes or ketones and allylic acetate (**63**), using an electrochemical process catalyzed by iron complexes (Table 2).

The reaction proved to be more complicated with aldehydes, due to pinacolization. Therefore, the addition of the aldehyde with a syringe pump is necessary. The authors demonstrated that allylic acetate (**63**) itself can serve as ligand instead of 2,2'-bipyridine (bipy). This fact proved that during the reaction allylic acetate coordinates to the iron salt, thus leading to an iron(I)-allyl acetate intermediate, which was probably transformed into a π -allyl iron complex before reacting with the carbonyl compounds.

With crotyl acetate (**65**) the reaction proved to be highly regioselective, furnishing almost exclusively branched homoallyl alcohols **66** (eq 14).

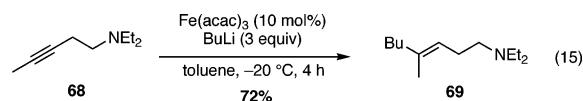


2.4. Carbometalations

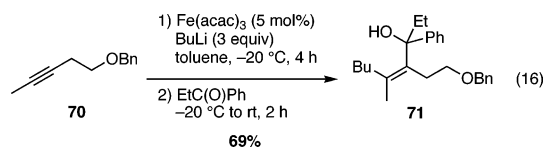
Another important class of carbon–carbon bond forming reactions to which iron catalysis has been applied is the carbometalation, namely, the addition of an organometallic reagent to an acceptor bearing a multiple C–C bond.

In some early attempts, iron(III) chloride has been used to catalyze the addition of tri-*iso*-butylaluminum to various alkynes.⁶³ The reaction was affected by several side processes, which considerably diminished its efficiency. Complex mixtures of products were obtained, including di- and trimerization adducts such as dienes and substituted aromatics.

The use of organolithium reagents instead of organoaluminum derivatives allowed obtaining much better results.⁶⁴ Thus, various substituted alkynes, bearing ethereal, benzylic and aryl functions, were easily transformed into the corresponding olefins in good to excellent yields. Notably, even a tertiary pentylamine could be converted under these conditions, giving **69** as single diastereoisomer (eq 15).



It is believed that the reaction involves an intermediate vinylolithium species. This hypothesis is substantiated by the possibility to quench the reaction with electrophiles, leading to tetrasubstituted olefins. Even a ketone could be used for this transformation, and the corresponding product **71** was isolated with complete stereoselectivity in good yield (eq 16).



Finally, the use of Grignard and organozinc reagents as nucleophiles has been reported by Nakamura and co-workers (see also paragraph 2.9, ring opening reactions). The latter organometallic reagents have been used in the iron-catalyzed carbometalation of very reactive olefins such as cyclopropenes.⁶⁵ An asymmetric version of this reaction has been developed employing chiral diphosphines as ligands (Table 3). High yields and good to excellent enantioselectivities were achieved.

In the iron-catalyzed enantioselective carbозincation reactions, (*R*)-*p*-Tol-BINAP proved to be the best ligand (entries 1–4). Changing the cosolvent from THP to THF caused a loss in yield, while the ee of the product was only barely diminished (entry 3 vs entry 4). Interestingly, the presence of TMEDA in the reaction mixture was essential. Although it decreased the reaction rate, racemic product was obtained in the absence of this additive (entry 7).

2.5. Nazarov Cyclizations

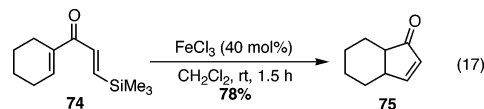
The Nazarov cyclization⁶⁶ is a powerful method to generate cyclopentene derivatives starting from divinyl ketones. This reaction is normally promoted by means of stoichiometric quantities of Lewis acids, and

Table 3. Enantioselective Carbозincation Reaction

entry	R ₂ Zn	ligand ^a	cosolvent	yield (%)	ee (%) (abs. conf.)
1	Pr ₂ Zn	A	THP	62	92 (<i>R</i>)
2 ^b	Et ₂ Zn	A	THP	64	90 (<i>R</i>)
3	Et ₂ Zn	A	THP	88	89 (<i>R</i>)
4	Et ₂ Zn	A	THF	73	85 (<i>R</i>)
5	Pr ₂ Zn	B	THF	82	71 (<i>R</i>)
6	Et ₂ Zn	B	THF	78	79 (<i>R</i>)
7 ^c	Et ₂ Zn	B	THF	69	0 (–)
8	Et ₂ Zn	C	THF	55	2 (<i>R</i>)
9	Et ₂ Zn	D	THF	73	13 (<i>S</i>)
10	Et ₂ Zn	E	THF	4	35 (<i>R</i>)

^a **A**: (*R*)-*p*-Tol-BINAP [(*R*)-2,2'-bis[bis(4-methylphenyl)phosphino]-1,1'-binaphthyl]; **B**: (*R*)-BINAP [(*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]; **C**: (*R*)-(*S*)-BPPFA [(*R*)-*N,N*-dimethyl-1-[(*S*)-1,2-bis(diphenylphosphino)ferrocenyl]ethylamine]; **D**: (*S,S*)-BPPM [(2*S*,4*S*)-*tert*-butyl-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)-1-pyrrolidine carboxylate]; **E**: (*R*)-(*S*)-PPFA [(*R*)-*N,N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine]. TMEDA (2.0–3.0 equiv with respect to alkylzinc) was present unless noted otherwise. ^b Large-scale experiment. ^c TMEDA was absent.

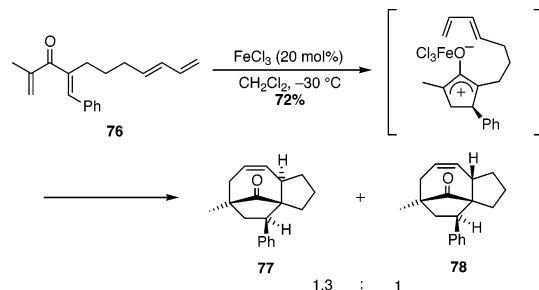
only isolated reports about the use of catalytic quantities of the latter are known.⁶⁷ Among them, some involve iron catalysts. In 1983, Denmark and co-workers employed anhydrous FeCl₃ to achieve the cyclization of ketone **74** possessing a vinylsilane moiety,⁶⁸ thus performing a silicon-directed Nazarov cyclization (eq 17). The advantages of this version in comparison to the classic one are that all side reactions are suppressed and only a single regioisomer of the final product is formed.



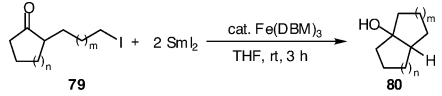
It should be noted that in this case the use of a stoichiometric quantity of the Lewis acid led to a similar result.

More recently, West and co-workers have shown that the same iron salt can be used to catalyze a Nazarov cyclization – [4+3] cycloaddition sequence, providing a rapid and high-yielding entry to rather complex polycyclic compounds **77–78**, which were obtained as a mixture of stereoisomers (Scheme 10).⁶⁹

Scheme 10



Also this reaction could be performed either in the presence of a catalytic or a stoichiometric amount of FeCl₃, giving identical results.

Table 4. Iron-Catalyzed Intramolecular Barbier Reaction


entry	<i>n</i>	<i>m</i>	yield (%) ^a	<i>cis/trans</i>
1	1	1	90 (60)	>99.5:<0.5
2	2	1	100 (75)	1.3:1
3	3	1	85 (77)	2.0:1
4	1	2	67	18:1
5	2	2	95 (75)	1:1.3
6 ^b	2	2	71	1:3.0
7 ^c	2	2	68	1:5.6

^a GC yield (yield). ^b The reaction was performed without catalyst. ^c The reaction was performed without catalyst and with YbI₂ instead of SmI₂ as reducing agent.

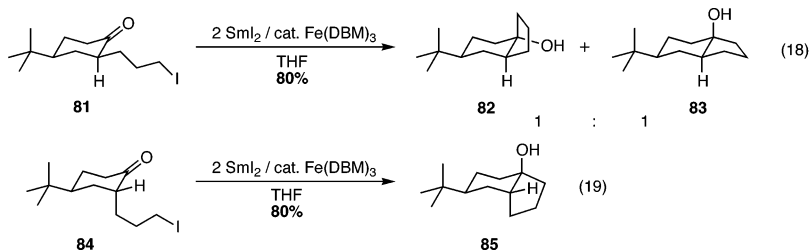
2.6. Barbier-Type Reactions

The Barbier reaction has been largely used in organic synthesis to generate alcohols starting from carbonyl compounds, employing alkyl and aryl halides in the presence of various reducing agents, such as alkali- and alkaline-earth metals, or lanthanide salts.^{70,71} The latter, in particular, SmI₂ and YbI₂, have been used under iron catalysis to promote various types of intramolecular Barbier-type reactions. The results of these studies have been presented in a series of papers by Molander and co-workers.^{72–76}

First, the synthesis of bicyclo[*m.n.0*]alkan-1-ols **80** has been achieved using SmI₂ in the presence of a catalytic amount of iron(III).^{72,73} The presence of the additional metal enhances the reaction rate. In some cases, however, the diastereoselectivity of the process proved to be superior in the absence of the catalyst, even if this issue appeared to be strongly dependent on the nature of both the substrate and the reducing agent (Table 4, see in particular entries 5–7).

In contrast, the nature of the iron species did not affect considerably the result of the reaction, the same results being obtained with a range of compounds such as FeCl₃, FeCl₂, and Fe(acac)₃. The choice of using Fe(DBM)₃ (DBM = dibenzoylmethane) was motivated by the fact that it is an air-stable, THF-soluble, and nonhygroscopic salt that can be easily prepared on a multigram scale.

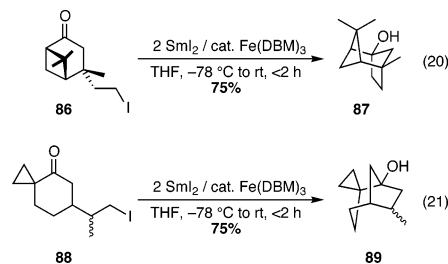
Substituents on cyclic substrates have a definite effect on the stereoselectivity. Very interesting is the case of 2-(3-iodopropyl)-4-*tert*-butylcyclohexanones (**81–84**; Scheme 11). While the *cis* substrate provides under the normal reaction conditions equimolar amounts of the two possible diastereomeric products (eq 18), the *trans* isomer undergoes cyclization with

Scheme 11

complete diastereoselectivity, giving only *cis* bicyclic product **85** (eq 19).

Interestingly, also the presence of a second substituent at position 2 of the ring was tolerated allowing products with complete diastereoselectivity to be obtained.

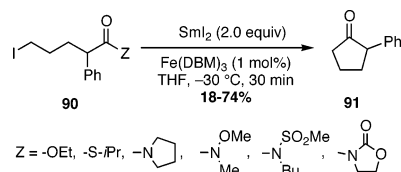
The conditions described above were applied to the synthesis of bicyclo[*m.n.1*]alkan-1-ols **87** and **89** as well. Now, 3-iodoalkyl cyclic ketones **86** and **88** were the starting materials (Scheme 12).⁷⁴

Scheme 12

The reaction is amazingly general, and very strained structure could be synthesized in this manner (Scheme 12). Due to the mild reaction conditions, functional groups such as alcohols, esters, double bonds, and strained carbocycles are tolerated.

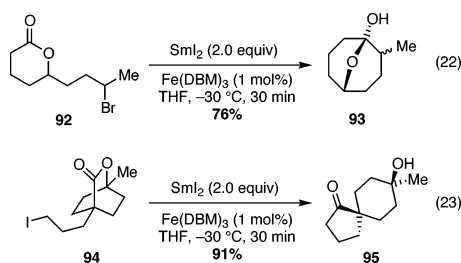
Unfortunately, although the excellent results obtained in the synthesis of bicyclo[*m.n.0*]alkanols and bicyclo[*m.n.1*]alkanols, the method could not be extended to the preparation of compounds having a two-carbon bridge. Thus, when 4-(2-iodoethyl)cyclohexanone was subjected to the standard reaction conditions, no trace of the desired bicyclo[2.2.2]octan-1-ol was detected in the mixture of products.

This methodology has also been extended to the use of electrophiles other than aldehydes and ketones.⁷⁵ Various acyclic acyl derivatives **90** such as esters, amides, and others were smoothly converted into the corresponding cyclization product **91** (Scheme 13).

Scheme 13

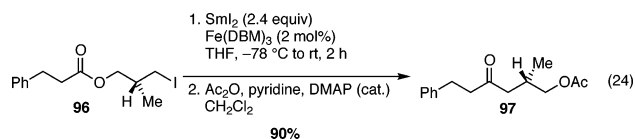
The reaction works also when lactones are used as substrates. In this case, the transformation can be regarded as the final step of a potentially useful multistep ring expansion sequence.

Scheme 14



Interestingly, conversely to the systems employing alkali- or alkali-earth metals as reducing agents (which involve a metal–halogen exchange) secondary halides such as **92** can be utilized in the SmI_2 – Fe –(III) mediated reaction as well (Scheme 14). The resulting hydroxyketone, formed as a 1.7:1 mixture of diastereomers, is in equilibrium with the hemiketal form **93**, which is thermodynamically favored. A further remarkable feature of this methodology is the possibility to easily access spirocyclic products, generally in high yields and often with complete diastereoselectivity (eq 23).

A useful complement of this intramolecular nucleophilic acyl substitution is the conversion of 3-iodopropyl carboxylates into 4-hydroxy ketones (eq 24).⁷⁶ Once again, good to high product yields could be obtained for a large number of substrates, and when chiral enantiopure starting materials were employed, an almost complete stereoconservation was observed ($ee \geq 95\%$). Thus, this reaction could also find application in the synthesis of natural products. For example, the formal synthesis of the vitamin E side chain was achieved in this manner.⁷⁶



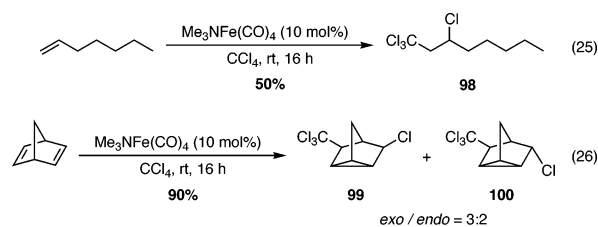
2.7. Additions of Halocarbons to Double Bonds (Kharasch Reaction)

The addition of polyhalogenated compounds to alkenes has received considerable interest as a method to form new carbon–carbon single bonds, after the discovery by Kharasch and co-workers that various halocarbons were able to give additions to olefins in a radical chain process.⁷⁷ The transformation can be catalyzed by a large number of transition metal complexes, among which iron compounds were found to be particularly efficient.

Various iron carbonyl complexes can act as catalysts for the addition of CCl_4 and CCl_3Br to simple olefins, the best being $\text{Me}_3\text{NFe}(\text{CO})_4$, which can readily be obtained by reaction of $\text{Fe}(\text{CO})_5$ with Me_3NO .⁷⁸ Interestingly, with norbornadiene as substrate a strained tricyclic compound is formed in high yield, albeit as a mixture of diastereomers (Scheme 15, eq 26).

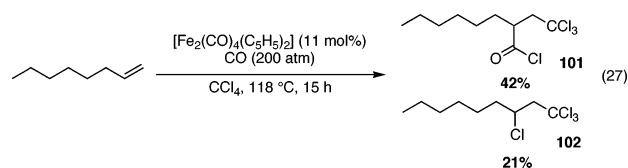
The reaction of simple alkenes with halocarbons can also be catalyzed by binuclear iron(II) species, such as $[\text{Fe}_2(\text{CO})_4(\eta\text{-C}_5\text{H}_5)_2]$, although in this case high temperatures (around 120°C) are required to obtain yields comparable to those achieved with the

Scheme 15

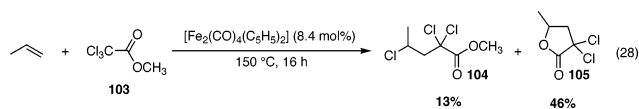


previous system. The process has been the subject of a kinetic study,⁷⁹ which revealed a linear dependence of the reaction rate upon the concentration of both the iron complex and of the halocarbon, and a more complex dependence upon the concentration of the alkene. These findings have been interpreted in terms of a mechanism that involves catalysis by an intact dinuclear species, but that also involves free radical intermediates.

Interestingly, when run under a high pressure of carbon monoxide, the Kharasch reaction offers the possibility to prepare acyl chlorides starting from alkenes (eq 27).⁸⁰ It should be noted, however, that a certain quantity of the normal addition product **102** is always produced together with the desired acyl derivative **101**.



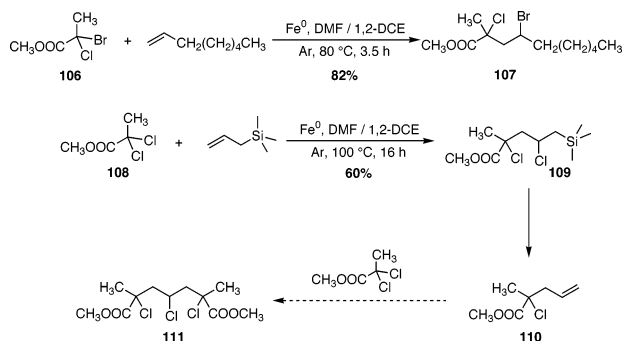
As expected, polyhalogenated compounds such as α -di or trihalo-substituted acyl derivatives, in particular esters, have the same or even higher reactivity than CCl_4 , and they also add to olefins. For example, the addition of methyl trichloroacetate (**103**) to propylene furnished a mixture of the expected addition product **104** and lactone **105** (eq 28).⁸¹



The composition of the mixture of products is strongly influenced by the catalyst. Thus, use of cobalt octacarbonyl leads to the selective formation of the acyclic addition product, while use of $[\text{Mo}_2(\text{CO})_6(\text{Cp})_2]$ results in the almost exclusive formation of the lactone. Similar results have been obtained by Freidlina and Velichko for the addition of α, α -dibromo and α, α, α -tribromoesters to activated olefins (acrylic acid derivatives) catalyzed by either FeCl_3 or $\text{Fe}(\text{CO})_5$.⁸² Also in this case, a mixture of the linear adduct and the lactone derived from the formal elimination of alkylbromide was obtained. Changing the reaction conditions allowed varying the ratio between the two products.

Iron has also proven to be active in promoting this class of additions in the elemental form. A catalytic amount of iron filings has in fact been used to catalyze the addition of α, α -dihalocarboxylates to simple olefins (Scheme 16).⁸³

Scheme 16

Table 5. Iron(II)-Catalyzed Cyclization of Olefinic α,α -Dichloro Esters

entry	n	R	cat (mol %)	time (h)	yield (%) ^a			
					<i>trans</i> - 113	<i>cis</i> - 113	<i>cis</i> - 114	<i>trans</i> - 114
1	1	Et	5.7	8	51	24		
2	1	Et	12	16	44	12	6	
3	1	Et	3.7	20	53	10		
4	1	Et	5.6	30	26	45		
5	1	Et	4.2	40	48	11		
6	1	H	4.0	24			66	
7	2	Et	4.2	40	23	40	7	3
8	2	H	8.2	24			35	15

^a Yields were determined by GLC. All compounds were then isolated in pure form and characterized.

Conditions such as temperature and solvent strongly affect the result of the reaction, which also depends on the iron particle size. The exceeding number of radicals produced by iron powder leads to worse results as a consequence of the increased number of side reactions. Furthermore, the method finds a severe limitation in the fact that only terminal olefins are reactive enough to ensure a good yield of the product.

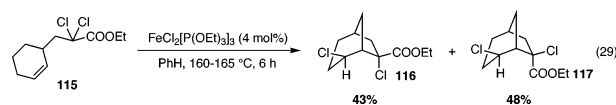
When allyltrimethylsilane is used as alkene, an allylation of the starting ester is observed. This transformation is illustrated in Scheme 16. As a result of an easy dehydrochlorination of intermediate **109**, ester **108** is finally converted into **110**. A second addition of **108** to allylic derivative **110** can then be avoided by working with an excess (more than 2 equiv) of allyltrimethylsilane.

The development of an intramolecular version of the Kharasch reaction has been achieved by Weinreb and co-workers, who reported about its synthetic potential in a brief series of papers.^{84–87} First, the cyclization of α,α -dichloro esters and acids bearing a double bond in a suitable position was addressed.^{84,85} Among various metal complexes, $\text{FeCl}_2[\text{P}(\text{OEt})_3]_3$ showed a remarkable capability to promote this reaction (Table 5). The products resulted almost exclusively from the *exo* cyclization of the starting material.

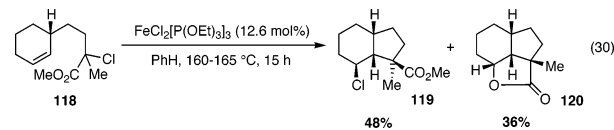
As can be seen from the data presented in Table 5, esters afforded monocyclic products *trans*-**113** and *cis*-**113** with almost complete selectivity. (The only

exceptions being the results shown in entry 2 and 7.) In contrast, the corresponding acids led exclusively to lactones *cis*-**114** and *trans*-**114** (entries 6 and 8). The formation of the two diastereomers of **113**, as well as the occurrence of the unique lactone **114**, was attributed to an equilibration involving an ester radical as intermediate.⁸⁵

This methodology also offers the possibility to access interesting bridged bicyclic compounds, provided that the starting materials possess a cyclic alkene moiety with the double bond in a suitable position (eq 29).⁸⁵

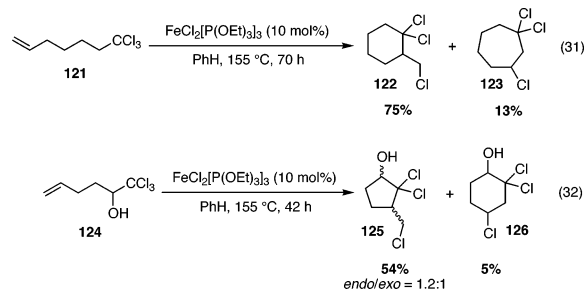


Weinreb and co-workers also demonstrated that mono- α -haloesters could be converted to the corresponding products by this kind of intramolecular transformation.⁸⁶ Considering the lower reactivity of the substrates in comparison to those previously described, longer reaction times and higher catalyst loadings were generally necessary to achieve useful yields of the final cyclic compounds. Moreover, with esters as starting materials the formation of considerable amounts of lactone **120** could not be avoided (eq 30).



(Trichloromethyl)alkenes have also been used in this kind of intramolecular cyclization.⁸⁷ Again, the previously shown ferrous catalyst performed well, being able to promote the reaction. Generally, good yields have been achieved, although in some cases long reaction times were required. Substrates bearing diverse functional groups such as alcohols, silyl ethers, and ketones reacted well (Scheme 17), and

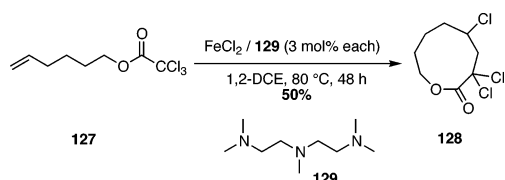
Scheme 17



some substituents showed interesting effects on the selectivity of the reaction.

As in the previously reported examples, the products arising from the *exo*-cyclization were generally predominating. In contrast, (trichloromethyl)alkenes bearing a carbonyl group in the α -position afforded mostly *endo*-products. This result was consistent with previous observations concerning the cyclization of simple non-chlorinated α -keto radicals.⁸⁸ Thus, the hypothesis of radical pathways in these reactions was further substantiated.

Scheme 18



Substrates with a silyl ether moiety failed to react with iron, and could be converted only by using $\text{RuCl}_2(\text{PPh}_3)_3$ as catalyst. (Dichloromethyl)alkenes, even when possessing keto functionality in the α -position, gave no reaction at all. This result was particularly puzzling, considering the good reactivities of α,α -dichloro esters and nitriles as well as even mono- α -chloro esters under the same reaction conditions (Table 5 and eqs 29–30).

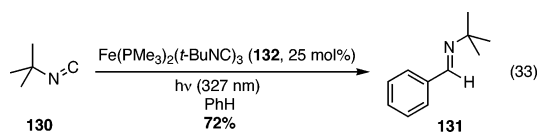
The latest improvement of this methodology has been realized by the use of nitrogen-based ligands together with simple metal salts as catalysts (usually CuCl and FeCl_2).⁸⁹ The amount of metal could thereby be considerably lowered, and the development of milder reaction conditions led to the products without any loss in yield. This approach is of particular interest for the synthesis of macrocycles, where it has been suggested that the metal acts as template, which enhances the rate of the cyclization process by bringing together the two reactive centers (the C=C double bond and one of the C–Cl bonds) (Scheme 18).

It should be noted that also in this case the product shown in Scheme 18 derives from the *endo* pathway (for a discussion of the competition between the two modes of cyclization, see ref 89b). The presence of a poly(ethyleneglycol) chain in the unsaturated moiety of the substrate allowed the preparation of macrocyclic lactones with up to 18 atoms in the ring.^{89b} In this case, FeCl_2 was the salt of choice, performing much better than the corresponding Cu(I) species, which was probably due to the higher solubility of the resulting complex and a superior template effect due to the higher acidity of iron(II).

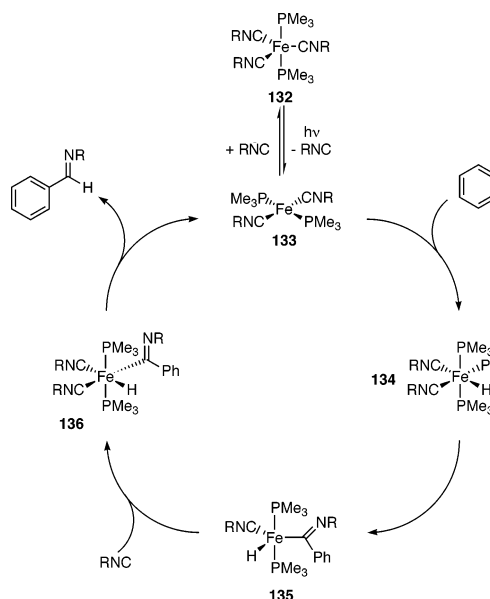
2.8. Addition by Means of C–H Activation

The activation of unreactive C–H bonds, such as the ones found in aliphatic and aromatic hydrocarbons, by means of homogeneous metal complexes is a field of major interest in nowadays organic chemistry, due to the possibility that it offers to access new organometallic species and new reactions.⁹⁰

The only iron-catalyzed activation of an unreactive C–H bond has been reported by Jones and co-workers in 1987.⁹¹ They found that iron(0) complex $\text{Fe}(\text{PMe}_3)_2(t\text{-BuNC})_3$ (**132**) was capable of promoting the addition of *tert*-butylisocyanide to benzene, toluene, and xylene under UV irradiation, to yield aldimines as final products (eq 33).



Scheme 19



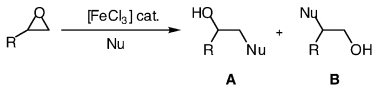
The proposed mechanism is showed in Scheme 19. The irradiation is fundamental, since the catalysis stops if it is discontinued. It has therefore been suggested that light provokes the dissociation of an isocyanide ligand, giving low-valent electron-rich intermediate **133** as the actual catalyst of the reaction. The sequence of events then continues with the oxidative addition of iron complex **133** to benzene, followed by insertion of an isocyanide molecule into the now reactive C–Fe bond, coordination of a new isocyanide unit, and final reductive elimination to furnish the product together with the catalyst, which will then undergo a further cycle.


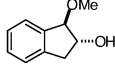

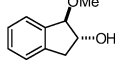




Although it is known that $\text{Fe}(\text{PMe}_3)_2(\text{RNC})_3$ and other iron complexes such as $\text{Fe}(\text{dmpe})_2$ ⁹² are able to undergo oxidative addition to alkanes, no report on the iron-catalyzed direct functionalization of alkanes has appeared so far.

2.9. Ring Opening Reactions

The opening of oxiranes catalyzed by Lewis acid has been widely studied. Iranpoor et al. have demonstrated that iron(III) chloride is efficient for this purpose.⁹³ With a catalytic quantity of anhydrous FeCl_3 (<15%), mono- and disubstituted epoxides are solvolyzed in alcohols to afford alkoxyalcohols in good to excellent yields (Table 6).^{93a} Advantageously, the reaction can be performed using $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ supported on silica, which is easier to handle giving equivalent or superior results.^{93b} In this latter case, water, acetate, halides, and nitrate also act as effective nucleophiles (Nu) for the opening of epoxides when using 30–40 mol % of $\text{FeCl}_3/\text{SiO}_2$ (Table 6). This iron-supported catalyst is then superior to other Lewis acids ($\text{BF}_3 \cdot \text{OEt}_2$, SnCl_4 , and FeCl_3) that are unable to promote oxirane-opening by bromides and chloride ions.^{93b} Starting from various types of epoxides, the reaction proceeds with the usual regio- and stereoselectivity, and the opening products are obtained with good to high yield (54–95%).

Whereas the precise role of the iron catalysts in the promotion of the opening of oxiranes is not well

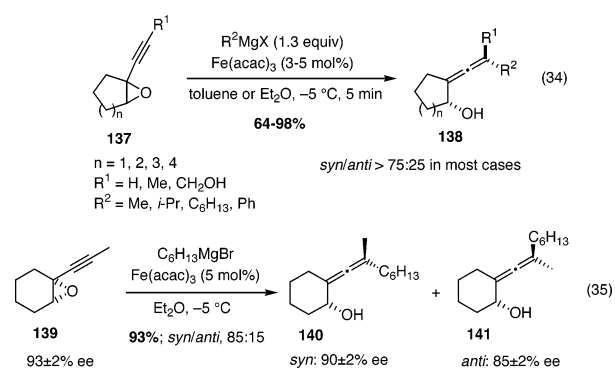
Table 6. Iron-Catalyzed Openings of Epoxides^a


entry	R or epoxide	Nu	cat. (mol%)	temp. (°C)	time (h)	product	yield (%)
1	Ph	MeOH	FeCl ₃ (5)	25	0.75	B	90
2	Ph	MeOH	FeCl ₃ /SiO ₂ (5)	25	0.25	B	95
3 ^b	Ph	H ₂ O	FeCl ₃ /SiO ₂ (20)	25	2	B	85
4	Ph	Cl ⁻	FeCl ₃ /SiO ₂ (40)	80	2	B	86
5	Ph	Br ⁻	FeCl ₃ /SiO ₂ (40)	25	6	B	85
6	ClCH ₂	MeOH	FeCl ₃ (15)	65	2.5	A	65
7	ClCH ₂	Br ⁻	FeCl ₃ /SiO ₂ (30)	25	12	A	90
8	ClCH ₂	NO ₃ ⁻	FeCl ₃ /SiO ₂ (30)	80	4	A	54
9	PhOCH ₂	<i>i</i> -PrOH	FeCl ₃ (5)	85	1	A	95
10	<i>i</i> -PrOCH ₂	EtOH	FeCl ₃ (5)	80	1.75	A	90
11		MeOH	FeCl ₃ (10)	25	0.5		85
12		MeOH	FeCl ₃ /SiO ₂ (10)	25	0.5		86
13		Br ⁻	FeCl ₃ /SiO ₂ (30)	25	8		77
14 ^c		AcOH	FeCl ₃ /SiO ₂ (30)	80	4		78

^a The epoxides openings by alcohols were performed in the corresponding alcohol as solvent. Opening reactions by bromide, chloride, and nitrate ions were performed by using the corresponding tetrabutylammonium salt (3 equiv) in anhydrous MeCN. ^b Performed in H₂O/MeCN (1:1). ^c Performed in AcOH.

defined, some experiments have shown that radical species were formed during the course of the reaction.^{93a} When the alcoholysis of epoxides is performed in the presence of acrylamide, polyacrylamide formation and a considerable decrease of the reaction rate were observed. It is therefore not surprising that prior attempts to perform asymmetric versions of the reaction afforded products with very low ee.⁹⁴

Although the formation of allenes by reacting Grignard reagents with propargyl halides in the presence of a catalytic amount of an iron salt was described by Pasto et al. 25 years ago,⁹⁵ almost no further development of this chemistry appeared in the literature.⁹⁶ However, in the fall of 2003 Fürstner and Méndez described a remarkable iron-catalyzed procedure to afford 2,3-allenol derivatives **138** from propargyl epoxides **137** and organomagnesium re-

Scheme 20

agents (Scheme 20).⁹⁷ These reactions have many advantages: they are virtually instantaneous, even at low temperatures (≤ 5 min), the required catalyst loading is low (≤ 5 mol %), no extra ligand is necessary, the yields are good to excellent (64–98%), and the substrate scope is sufficiently broad. Moreover, the direct attack of the Grignard reagent at the epoxide ring remains insignificant in all but the most activated cases. Remarkably, the *syn*-configured 2,3-allenols **138** are invariably formed as major products (best results are obtained in toluene), which is the opposite stereochemical outcome to the one usually observed with organocopper reagents (except when carried out under “ligand-free” conditions in the presence of an excess of TMSCl).⁹⁸ Interestingly, with optically active epoxides such as **139**, the central chirality of these substrates is transferred to the axial chirality of the resulting allenols **140–141** with high fidelity (Scheme 20, eq 35).

The utility of metal-catalyzed regio- and stereoselective ring-opening reactions of oxabicyclic alkenes in the synthesis of cycloalkenols has been demonstrated in various examples.⁹⁹ Arylative and alkenylative ring-opening reactions of [2.2.1]- and [3.2.1]-oxabicyclic alkenes by Grignard reagents (2 equiv) take place, in the presence of a catalytic amount of iron(III) chloride (5 mol %) and a stoichiometric quantity of TMEDA, to produce highly substituted 3-cyclohexen-1-ol or 3-cyclohepten-1-ols in good yields and with high regio- and complete stereoselectivity (Table 7).¹⁰⁰ While in the absence of the iron catalyst no reaction occurs, the use of TMEDA is not indispensable, but its presence increases the reaction rate.

The reaction takes place in such a manner that the nucleophile attacks the carbon–carbon double bond from the *exo*-face of the substrate to give the corresponding *all-cis*-substituted cycloalkenol after subsequent β -eliminative ring opening of the oxo-bridge. Moderate to good yields of the substituted product have been obtained with vinyl- and phenylmagnesium bromides as nucleophiles (41–80%, entries 1, 2, 5–7). Conversely, surprising results have been observed with alkyl Grignard reagents (entries 3 and 4). Thus, use of *n*-C₁₄H₂₉MgBr afforded the product of 2-tetradecenyl group transfer, which suggested the intervention of a β -hydride elimination with the formation of a 2-metallo-1-alkenyl species (entry 3). When a secondary alkyl Grignard reagent such as *i*-PrMgBr was allowed to react with the substrate, hydride reduction takes place with complete regio-

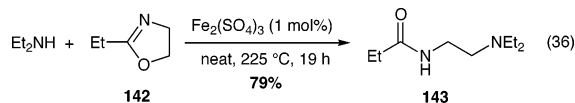
Table 7. Iron-catalyzed Ring Openings of Oxabicyclic Alkenes by RMgBr^a

entry	substrate	RMgBr	product	yield (%)
1		Ph		74
2		H ₂ C=CH		41
3		<i>n</i> -C ₁₁ H ₂₃		54
4		<i>i</i> -Pr		92
5		Ph		80
6		Ph		54
7		Ph		67

^a Reactions performed with FeCl₃ (5 mol %), RMgBr (2 equiv), and TMEDA (3 equiv) in THF at 25–65 °C for 1–13 h.

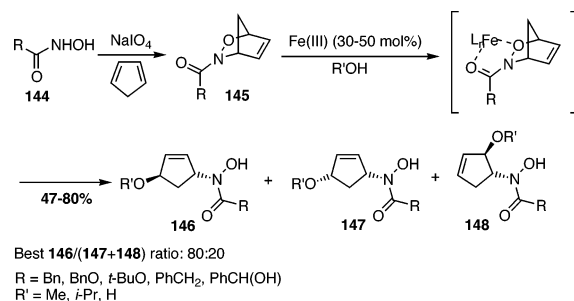
and stereoselectivity affording the product in excellent yield (92%, entry 4). To explain the reaction mechanism, two pathways have been envisaged: carbometalation/ β -oxygen elimination or oxidative addition/ π -allylmetal formation.¹⁰⁰

Opening reactions of other heterocycles have also been described. For example, oxazolines can be opened by a secondary amine in the presence of a catalytic amount of iron(III)sulfate (1 mol %). In the conversion of **142** this opening leads to the formation amino amide derivative **143** with 79% yield (eq 36).¹⁰¹



The nucleophilic attack occurs only at position 5 affording the 2,2-disubstituted protected ethylenediamine. However, harsh conditions are required for this transformation (225 °C, neat).

Hydroxamic acids are interesting compounds, especially in view of their possible biological applications as inhibitors of metal-containing enzymes.¹⁰² Surman and Miller reported that treatment of acylnitroso hetero Diels–Alder cycloadduct **145** with iron(III) salts (FeCl₃, Fe(III)citrate; 30–50 mol %) in protic medium (alcohol or water) induces ring opening to afford predominantly *anti*-1,4-disubstituted cyclopentenes **146** while regenerating an hydroxamic

Scheme 21

moiety (Scheme 21).¹⁰³ However, the stereoselectivity is often moderate.

It has to be noted that the regioselectivity is not always predictable, and that when copper(II) or palladium(0) catalysts are used instead of iron(III), stereoisomer **147** is generally the major product.^{103a}

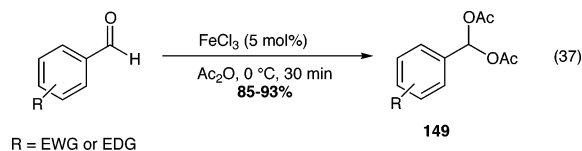
2.10. Acetalizations and Related Protection Methodologies

Iron-catalyzed reactions have also found application in the vast field of protective group chemistry,¹⁰⁴ especially as far as the protection of carbonyls or, on the other hand, diols as acetals or similar compounds is considered.

Iron(III) chloride has been used as catalyst to protect sugars as isopropylidene¹⁰⁵ or methylene acetals.¹⁰⁶ In both cases, the 1:2 adducts between the sugars and the carbonyl compounds (acetone¹⁰⁵ or formaldehyde¹⁰⁶) were obtained as products. In the last case, the yields are only moderate, but they can be raised by making use of a heterobimetallic catalytic system, generated by adding FeCl₃ and SnCl₂·H₂O in a 1:4 molar ratio to the reaction mixture.

An easy protection of a large array of aldehydes and ketones as thioacetals has been achieved by using FeCl₃ (20–40 mol %) dispersed on silica gel.¹⁰⁷ Notably, the yields of the products are almost quantitative in all cases, and the reaction often takes place instantaneously, with reported reaction times shorter than one minute.

A transformation related to the acetalization is the conversion of carbonyls into geminal diesters, or acylals, which can be preferred to acetals as protecting groups due to their superior stability in neutral and basic media.^{104b} Also in this case anhydrous FeCl₃ has been shown to be very efficient in catalyzing the reaction. Thus, acylals **149** of various aldehydes could be prepared by reaction with acetic anhydride under mild conditions (eq 37).¹⁰⁸

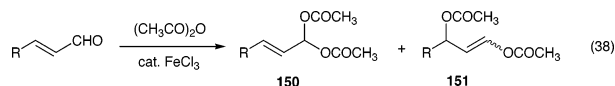


With aromatic aldehydes, the results were particularly remarkable, but the method worked also well with aliphatic and α,β -unsaturated substrates.

An improvement based on the dispersion of the catalyst on montmorillonite has been successively reported.¹⁰⁹ The catalyst loading could be reduced (to

1.5 mol %) and the reaction times were shortened, working at room temperature. The method is general for aldehydes, but usually fails in the protection of ketones or cyclic anhydrides.

Finally, Trost and Lee made use of anhydrous iron trichloride as catalyst for the transformation of various α,β -unsaturated aldehydes into acylals **150**, which were required as substrates in an investigation on the asymmetric allylic alkylation of geminal dicarboxylates with dialkyl malonates.¹¹⁰ The method gave good results with all substrates, although the authors reported that iron(III) chloride is able to

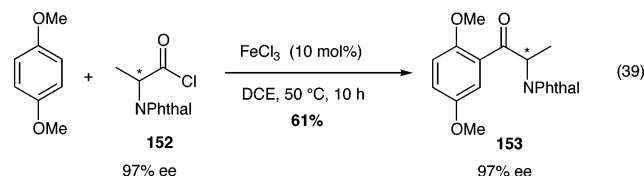


catalyze the rearrangement of **150** to vinyl acetate **151** as well (eq 38). For this reason, and because the successive experiments would have been considerably complicated by the presence of the chiral racemic vinyl acetate, the reactions were often quenched before complete consumption of the starting material.

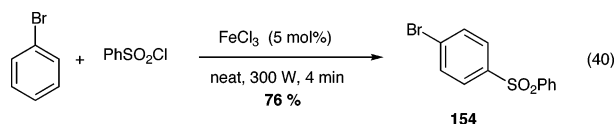
3. Substitution Reactions

3.1. Electrophilic Substitutions

Iron(III) chloride has been widely used as Lewis acid for electrophilic aromatic substitutions,¹¹¹ and it is one of the best catalysts known for this reaction. The Friedel–Crafts¹¹² alkylations¹¹³ and acylations¹¹⁴ of arenes have been the most studied reactions. Iron(III) chloride is especially efficient for the latter reaction, but long reaction times are often required. For example, *p*-methoxyanisole reacts with optically



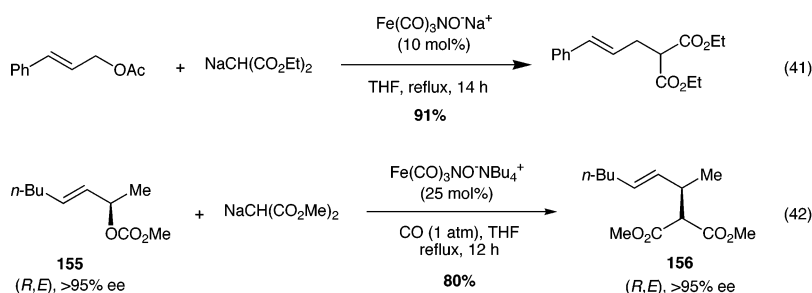
active acyl chloride **152** to afford the corresponding ketone in 61% yield. Racemization was not observed



(eq 39).^{114b} When AlCl_3 or SnCl_4 were used, the product yields were significantly lower.

Under microwave irradiation (MW) the Friedel–Crafts acylation with FeCl_3 proceeds in a very fast

Scheme 22



manner (some minutes), which allows even less reactive arenes to react.¹¹⁵ This very efficient MW process works also for the sulfonylation of aromatic substrates (eq 40).¹¹⁶ For example, bromobenzene reacts with phenyl sulfonyl chloride in 4 min under 300 W irradiation and affords exclusively the para-substituted product **154**. Under these conditions, even the electron-poor fluorobenzene is able to react. As an alternative, the sulfonylation of electron-rich aromatics can be performed with an iron(III)-montmorillonite catalyst in nitrobenzene (at 120–200 °C).¹¹⁷

Iron(III) chloride (10 mol %) is also able to catalyze the halogenation of aromatic arenes with *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimide (in refluxing acetonitrile as solvent). Even with electron-poor substrates the products are obtained in good yields. Strong Lewis acids, in contrast, show low efficiency. Unfortunately, the FeCl_3 -catalyzed reaction is rarely selective.¹¹⁸

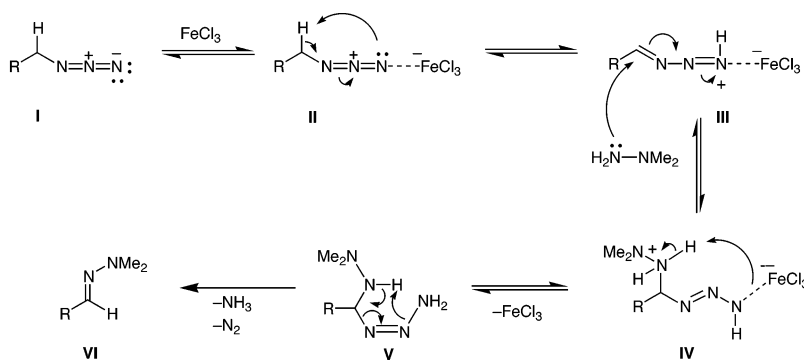
3.2. Nucleophilic Substitutions

3.2.1. S_N Processes

The high efficiency of allylic substitutions and the excellent results obtained in its asymmetric version make it a powerful reaction for C–C bond formations.¹¹⁹ Various transition metals salts have been found to catalyze this transformation,¹¹⁹ among which palladium is predominant.¹²⁰ Iron complexes are also capable of promoting this reaction.

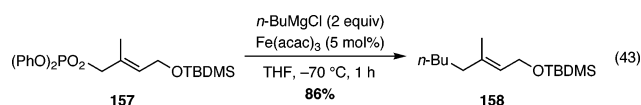
The substitution of allyl η^3 -iron complexes by a nucleophile occurs generally at the site of the leaving group. The iron complexes used in these reactions are mainly carbonyl derivatives, which are known to be good precursors for allylic complexes (Scheme 22).¹²¹ Diiron nonacarbonyl $[\text{Fe}_2(\text{CO})_9]$ is active in this transformation, and it has been used in several mechanistic and selectivity studies. Generally, however, it gives worse control (mixture resulting from both S_N2 and S_N2' reactions)¹²² than its isoelectronic analogue, tricarbonyl nitrosyl ferrate $[\text{Fe}(\text{CO})_3\text{NO}]^- \text{M}^+$. This latter catalyst has been studied with various counterions. With 10 mol % of $[\text{Fe}(\text{CO})_3\text{NO}]^- \text{Na}^+$, the substitution of phenyl allyl acetate by sodium diethylmalonate leads to only a single isomer.¹²³ The reaction occurs with total retention of configuration (eq 41). However, this process is highly dependent on the nature of the nucleophile and of the leaving group.^{122,123} The complex $[\text{Fe}(\text{CO})_3\text{NO}]^- (\text{NBu}_4^+)$ has also been used as catalyst in the alkylation of an optically enriched allylic carbonate **155**.¹²⁴ In this case, working under an atmosphere of carbon monoxide was required, since otherwise no reaction

Scheme 23

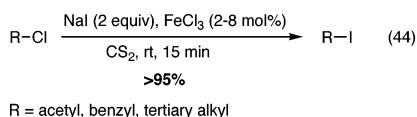


occurred. For substrates with an internal double bond, the substitution occurs predominantly in α position (S_N2) with complete retention of the configuration and in high yield (eq 42).^{124b}

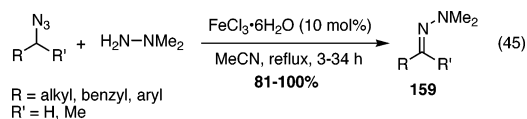
The commercially available iron salts $\text{Fe}(\text{acac})_3$ and FeBr_2 are useful catalysts for the substitution of allylic phosphates by diverse Grignard reagents (alkyl-, benzyl-, aryl-, and vinylmagnesium halides).¹²⁵ The yields are good (54–95%) and the S_N2/S_N2' ratios often reach 99:1 (eq 43).



Iron complexes have also been used to prepare iodo compounds from the corresponding chlorinated substrates (Finkelstein reaction). This reaction is performed in carbon disulfide or benzene at room temperature with 2 equiv of sodium iodide and gives rise to excellent yields of products (>95%) in a few minutes (eq 44).¹²⁶



More recently, iron trichloride has been used in the substitution of azide by dimethyl hydrazine, which allows the formation of hydrazones **159** in very good yields (>81%, eq 45).¹²⁷



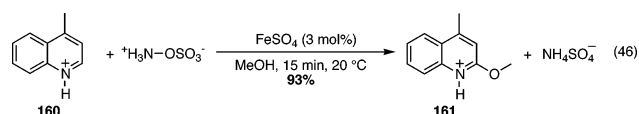
The reaction works with various azides. In the case of aromatic substrates the reaction times are shorter when the arenes bear electron-withdrawing substituents. The nature of the hydrazine has also been studied, and in the reaction of aryl hydrazine with benzyl azide, good yields are generally obtained within ca. 10 h. With arenes having electron-donating groups, decomposition of the hydrazone occurs. A possible mechanism for this substitution reaction is shown in Scheme 23.

Presumably, iron acts as a Lewis acid that promotes the tautomerization of azido species **I**, via **II**, to an imino type compound **III**, providing a good electrophilic substrate for the nucleophilic hydrazine.

An internal proton transfer in hydrazine adduct **IV** yields **V**, which upon expulsion of nitrogen and ammonia collapses to hydrazone **VI**.

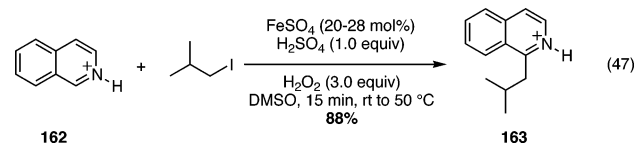
3.2.2. S_{RN} Processes

Another important methodology for the formation of carbon–carbon single bonds is the nucleophilic substitution carried out by radical intermediates. The radical can either act as the nucleophile,¹²⁸ in combination with a suitable electrophile, or be attacked by a nucleophile, so representing the electrophilic partner (in this case a $S_{RN}1$ reaction takes place).¹²⁹ The first class of reactions and the possibility of using iron-based catalysts has been investigated in detail by Minisci and co-workers, who, in particular, applied protonated heteroaromatic bases as electrophiles.¹³⁰ Interestingly, these reactions reflect many of the aspects of Friedel–Crafts-type aromatic substitutions, but with opposite reactivity and selectivity, due to the nucleophilic character of the radical species. Using hydroxylamine-*O*-sulfonic acid (HSA) as source of radicals in the presence of FeSO_4 , it is possible to achieve the 2-substitution of protonated 4-methylquinoline (**160**) in good yields (eq 46).^{130a} Noteworthy, the solvent is also the nucleophile in this case.



The role of iron in the reaction is believed to be the generation of $\text{NH}_3^{+\bullet}$ radicals from HSA, which will then react with the protic solvent RH to give R^\bullet radicals and ammonium ions. Using hydrogen peroxide or *t*-BuOOH as oxidants in the presence of aldehydes, the methodology has been extended to the regioselective acylation of other protonated heteroaromatic bases.^{130b} In these cases, acyl radicals are generated, which act as nucleophiles, and the above-mentioned analogy to Friedel–Crafts reactions is particularly evident here.

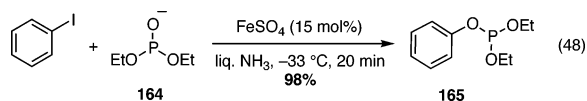
Later, an alkylation protocol based on the use of alkyl iodides in the presence of H_2O_2 and DMSO as solvent was developed (eq 47).^{130c}



Notably, DMSO acts not simply as the solvent, but also, within a rather complicated chain sequence, as a source of methyl radicals, which are able to homolytically abstract the iodine atom from the alkyl iodides, thus giving the alkyl radicals that then attack the electrophile. It should be noted that not only tertiary alkyl iodides, but also secondary and even primary iodides, can be used in this process, although in the latter cases modifications of the original procedure have to be introduced.

For the $S_{RN}1$ reaction, it is known that it occurs through a chain mechanism whose first step is represented by the generation of a radical anion from an aryl (or alkyl) halide, which captures an electron.¹³¹ Although this mechanism is occasionally spontaneously initiated, it generally requires a proper induction. For a number of years, photostimulation or electrochemical methods have been the only ones used for the purpose. Then it was found that iron(II) salts were able to catalyze $S_{RN}1$ reactions,¹³² and it was supposed that their role was to enhance the rate of the electron transfer toward the substrate.

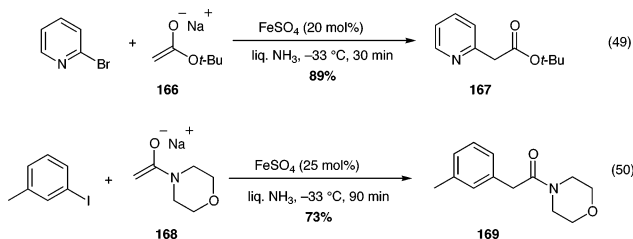
It was discovered that bromo- and iodobenzenes were able to react with strong nucleophiles such as enolate ions in the presence of a catalytic amount of $FeSO_4$ (typically 15 mol %). Also oxygen nucleophiles such as diethyl phosphite (**164**) proved to be active in such transformations (eq 48).



While iron(II) salts worked well in the reaction, iron(III) species completely failed in affording the products. The main disadvantage of this methodology is clearly the required use of liquid ammonia as the solvent. This problem can be circumvented by using DMSO at room temperature. Iron(II) chloride (40 mol %) is then the iron source of choice for obtaining good results. Conversely, employment of $FeSO_4$ as the catalytic species leads to low product yields, and large amounts of the substrate are recovered unmodified.¹³³

Almost contemporarily, it was shown that not only aryl, but also vinyl halides were able to react with enolates under iron catalysis to give $S_{RN}1$ processes.

Scheme 24



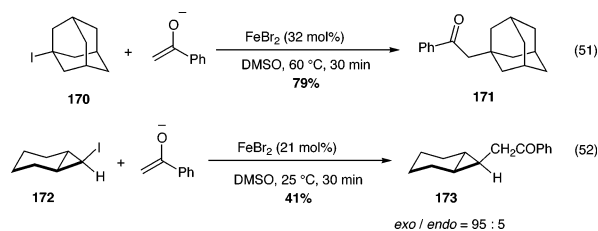
While the first findings appeared ambiguous,¹³⁴ subsequent systematic studies¹³⁵ clearly demonstrated that a radical $S_{RN}1$ pathway was only followed in the case of *conjugated* vinyl halides, while *unconjugated* substrates only provided products arising from different mechanistic routes.

Efforts to broaden the scope of this reaction have been made either by changing the nucleophilic¹³⁶ or

the electrophilic reagents. First, ester and amide enolates have been employed.¹³⁷ In the presence of iron(II) sulfate the corresponding products were usually obtained in good yield. Heteroaryl halides (Scheme 24) could also be applied, although substantial amounts of byproducts such as disubstituted esters or amides, or β -ketoesters were often detected in the crude reaction mixture. Moreover, in this case the use of DMSO as solvent was unsuccessful, thus forcing the reaction to be run in liquid ammonia at low temperature. *N*-Acetylmorpholine derivatives such as **168** were chosen because of their good solubility in ammonia and their ability to react with chloro- and bromobenzene under photostimulation.¹³⁸

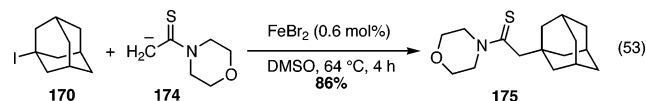
When searching for different electrophiles, Rossi and co-workers found that $FeBr_2$ was able to promote the reaction of ketone enolates with alkyl iodides, although in this case harsher reaction conditions were required, and sometimes the iron salt loading had to be increased (Scheme 25).¹³⁹

Scheme 25



Interestingly, when a 1:1 mixture of *endo:exo* isomers of 7-iodo norcarane (**172**) was used as substrate, the substitution product **173** was obtained largely as *exo* isomer, albeit in moderate yield. This result was consistent with those obtained under photostimulation and indicated the formation of a planar norcaryl radical during the course of the reaction. Since it could react with the nucleophile on both faces, it finally gave a large excess of the thermodynamically more stable *exo* product. A $S_{RN}1$ mechanistic pathway for this reaction was thus confirmed.

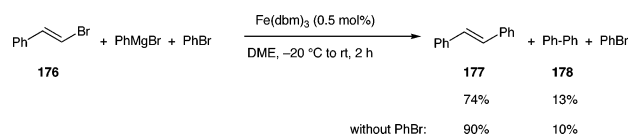
Finally, reactions of alkyl iodides such as iodoadamantane with α -alkylthioacetamides were studied.¹⁴⁰ Due to the high reactivity of the corresponding enolates, it was found that very low quantities of the catalyst ($FeBr_2$ in the present case) were sufficient to afford high yields of the substitution products (eq 53).



3.3. Cross-Coupling Reactions

The involvement of iron in cross-coupling reactions¹⁴¹ has recently caught much attention. In general, such carbon-carbon bond forming processes have evolved to a routine tool for the preparation of fine chemicals and pharmaceutically active compounds in the laboratory as well as on the industrial scale.¹⁴² While a large variety of organometallic reagents and organic electrophiles can be applied in cross-coupling processes, the field is largely dominated by the use of palladium and nickel complexes as catalysts.¹⁴³ As early as 1972 Corriu and Kumada

Scheme 26

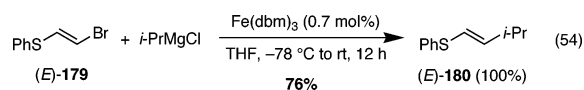


independently developed nickel-catalyzed coupling reactions of Grignard reagents with alkenyl and aryl halides.¹⁴⁴ Even a year before, however, Kochi had shown that iron salts could be used as catalysts for the same purpose.¹⁴⁵ These early cross-coupling examples were performed with vinyl bromide derivatives and alkyllmagnesium reagents, using iron(II) or (III) complexes as catalysts.¹⁴⁵

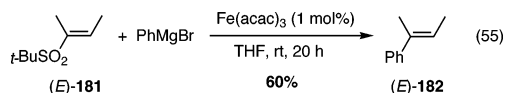
3.3.1. Alkenyl Derivatives as Substrates

Other examples of iron-catalyzed cross-couplings of vinyl halides with organometallic compounds (especially Grignard reagents) followed after these first reports.^{146–153} Interestingly, when the cross-coupling between phenylmagnesium bromide and *β*-styryl bromide (**176**) catalyzed by Fe(DBM)₃ was performed in the presence of bromobenzene, the reaction was completely selective for the coupling with the vinyl derivative providing *trans*-stilbene (**177**). Bromobenzene was recovered almost quantitatively, and only a small quantity of biphenyl (**178**) was detected under these conditions (Scheme 26).¹⁴⁶

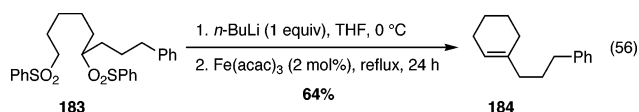
When bromothioethenes are used as substrates with *i*-PrMgCl and iron catalysts, the coupling is stereospecific, whereas mixtures of isomers are obtained with palladium or nickel catalysts (eq 54).¹⁴⁷



Such reactions also work with vinyl sulfones, but they often afford products as mixtures of *Z,E* isomers. Moreover 1,4-addition and reduction compounds are obtained in notable quantities.¹⁴⁸ In some cases, however, this method can give good results in terms of yield and selectivity, and iron(III)-catalyzed couplings such as the one between sulfone **181** and PhMgBr (eq 55)^{148a} have even been applied to the total synthesis of pheromones.^{148c}



It should also be noted that, in the presence of *n*-BuLi and the same catalyst, sulfones can undergo couplings to afford olefinic compounds (eq 56).¹⁴⁹



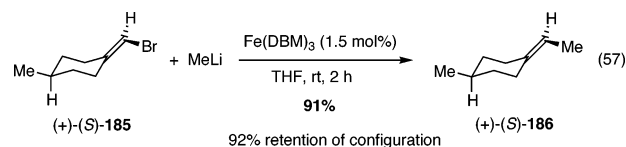
High selectivities and 92% retention of configuration have been achieved in transmetalations with organolithium reagents. Noteworthy, partial racem-

Table 8. Iron-Catalyzed Cross-Coupling Reactions of Grignard^a or Organomanganese^b Reagents (RMX) with Alkenyl Halides (R'X)

		$\text{RMX} + \text{R}'\text{X} \xrightarrow{\text{Fe(acac)}_3 \text{ cat.}} \text{R-R}'$	
entry	RMX	R'X	R-R' yield (%)
1			60
			69
2			60
3			73
4	<i>i</i> -PrMgBr		72
5	<i>n</i> -BuMgBr		80
6	MeMgBr		68
7	<i>n</i> -BuMgBr		79
8 ^c	<i>n</i> -BuMgBr		64
9 ^d	<i>c</i> -C ₆ H ₁₁ MgBr		82
10	<i>n</i> -BuMnCl		74

^a Reaction performed with RMgBr (1.4 equiv) and Fe(acac)₃ (5 mol %) in THF at $-20\text{ }^\circ\text{C}$ for 15 min (entries 1–3)¹⁵¹ or with RMgBr (1.1 equiv) and Fe(acac)₃ (1 mol %) in THF–NMP at $-5\text{ }^\circ\text{C}$ for 15 min (entries 4–7).¹⁵² ^b Reaction performed with *n*-BuMnCl (1.4 equiv) and Fe(acac)₃ (3 mol %) in THF at room temperature for 1 h (entry 10).^{153a} ^c Ref 155. ^d 3 equiv of RMgBr.¹⁵⁶

ization occurred, when cobalt or silver catalysts were applied (eq 57).¹⁵⁰



Very important contributions in the cross coupling of alkenyl halides with organometallic species stem from Cahiez. He greatly increased the scope of the reaction by demonstrating the possibility to react functionalized aryl Grignard reagents (also supported ones)¹⁵¹ and/or functionalized vinyl halides¹⁵² with Fe(acac)₃ as catalyst (Table 8, entries 1–7). In the last case, the use of NMP as solvent additive to THF led to very good results with ca. 80% yields of

Table 9. Iron-Catalyzed Cross-Coupling Reactions of Organometallic Reagents (RM) with Aryl and Heteroaryl Chlorides, Tosylates, and Triflates (Ar-X)^a

entry	Ar-X	RM	yield (%) of product Ar-R
1		<i>n</i> -C ₆ H ₁₃ MgBr	83 (X = OTs)
2		<i>n</i> -C ₆ H ₁₃ MgBr	87 (X = OTf)
3		<i>n</i> -C ₆ H ₁₃ MgBr	91 (X = Cl)
4		H ₂ C=CHMgBr	0
5		H ₂ C=CHCH ₂ MgBr	0
6		Et ₂ ZnMgBr	93
7		C ₁₄ H ₂₉ MnCl	96
8		(C ₁₄ H ₂₉) ₂ Mn	98
9		(C ₁₄ H ₂₉) ₂ MnMgCl	98
10		<i>n</i> -C ₄ H ₉ Li	0
11		EtMgBr	67
12		<i>n</i> -C ₁₄ H ₂₉ MgBr	72
13		PhMgBr	71
14			63
15			63
16 ^b		PhMgBr	45

^a Reactions performed with RM (1.2–2.3 equiv) and Fe(acac)₃ (5 mol %) at 0 °C or room temperature in THF/NMP for 10 min (entries 1–11) or in THF at –30 °C for 1 h (entries 11–16).¹⁵⁸ ^b Ref 159.

the cross-coupling products. In pure THF, less than 5% yield were obtained.¹⁵² The discovery of this solvent effect had significant consequences in the development of the process (vide infra). Indeed, those solvent conditions are also applicable to organomanganese reagents that can add to various vinyl halides, in the presence of catalytic amount of Fe(acac)₃ (3 mol %) at room temperature for 1 h. Usually, the yields and selectivities are good and many functional groups are tolerated (Table 8, entry 10).^{153,154}

All these reactions are stereospecific and occur with retention of configuration of the double bond.

The metal-catalyzed cross-coupling reaction of Grignard reagents with vinyl bromides has been the subject of a mechanistic study by Hoffmann et al.,¹⁵⁷ in which an enantiomerically enriched chiral organomagnesium species was used. On the basis of the partial racemization of the final product (compared to the ee of the starting material), a single electron transfer (SET) process was suggested to take place in the transmetalation step when Fe(acac)₃ was used as catalyst. Conversely, the use of Ni or Pd catalysts afforded the cross-coupling product without significant lowering of the ee.

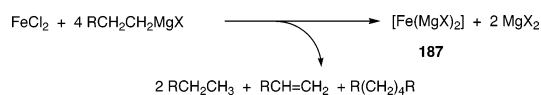
3.3.2. Aryl Derivatives as Substrates

Recently, Fürstner obtained excellent results in the cross-couplings of aryl halides with a broad range of organometallic reagents (Table 9).¹⁵⁸ With 5 mol % of an iron precatalyst (mainly Fe(acac)₃ for convenience, but also FeCl_x or Fe(salen)Cl) under mild conditions (rt or –30 °C, up to 98% yield in less than 1 h), this reaction gives good to excellent results with manganese, zinc, and magnesium derivatives (alkyl and aryl organic moiety) and functionalized aryl halides as substrates. Triflates and tosylates can also be used, whereas lithium derivatives and vinyl and allyl organometallic reagents (Table 9, entries 4, 5, and 10) are incompatible.¹⁵⁸ Even nonactivated aryl derivatives such as pyridines are reactive and afford satisfactory yields (45–72%). In some cases, the reactions occur in 15 min at room temperature when performed in THF/NMP as solvent.¹⁵⁸

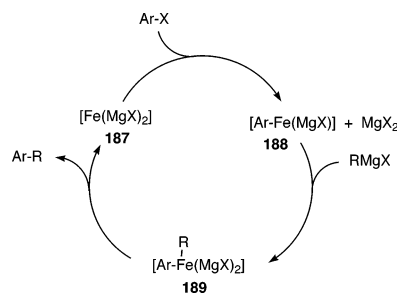
Without substantial modifications in the procedure, the method has been applied by Hocek and Dvůřáková in the monomethylation reaction of 2,6-dichloropurines with MeMgCl.¹⁶⁰ The reaction proceeded with complete regioselectivity, affording only the products of coupling in position 6 of the ring, with moderate to good yields (up to 72%).

On the basis of previous results Fürstner proposed the mechanism shown in Schemes 27 and 28.^{158b}

Scheme 27



Scheme 28



Since it is well established that FeCl₂ reacts with 4 equiv of RMgX to give an “inorganic Grignard reagent” [Fe(MgX)₂] (**187**),¹⁶¹ it is suggested that the reduction process leads to highly nucleophilic species with a formal negative charge at iron (Scheme 27).

The highly nucleophilic iron species **187** lacking any stabilizing ligands are able to oxidatively add to

Table 10. Iron-Catalyzed Cross-Coupling Reactions of Alkyl Halides (RX) with ArMgBr

entry	R-X	ArMgBr	method ^a	product	Yield (%)
1		Ph	A		99 (X = I, Br, Cl)
2		4-CF ₃ C ₆ H ₄	A		67 (X = Br)
3		<i>p</i> -tolyl	B		69 (X = Br)
4		Ph	A		94
5		<i>p</i> -tolyl	B		73
					97 (X = I)
6	<i>n</i> -Oct-X	Ph	A	<i>n</i> -Oct-Ar	91 (X = Br)
					45 (X = Cl)
					70 (X = Br)
7	<i>p</i> -tolyl		B		50 (X = OTs)
8		4-MeOC ₆ H ₄	A		91
				(<i>exo/endo</i> , 95:5)	
9		4-MeOC ₆ H ₄	A		88
10		4-MeOC ₆ H ₄	A		87

^a Method A: FeCl₃ (5 mol %), RX (1 equiv), ArMgBr (1.2 equiv, slow addition), and TMEDA (1.2 equiv, slow addition) in THF (-78 to 0° C), 0.5 h.^{164a} Method B: Fe(acac)₃ (5 mol %), RX (1 equiv) and ArMgBr (1.04 equiv) in refluxing Et₂O, 0.5 h.^{164b}

aryl halides. The resulting organometallic iron compounds **188** (formally Fe(0)) are alkylated by the excess of the Grignard reagent in analogy to the elementary steps passed through during the initial formation of **187** from FeCl₂ and RMgX. Subsequent reductive coupling of the organic ligands then forms the desired product and regenerates the propagating Fe(-II) species (Scheme 28).^{158b}

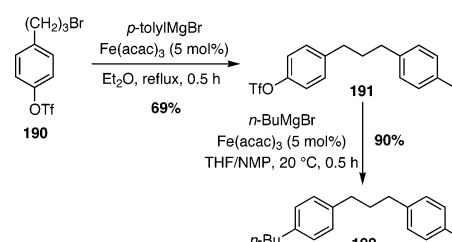
3.3.3. Alkyl Derivatives as Substrates

Some early examples of iron-catalyzed coupling reactions between Grignard reagents and alkyl halides have appeared in the literature,¹⁶² and homo-couplings and conversions of the alkyl halides into the corresponding alkenes and alkanes are (in the case of primary and secondary alkyl halides) the most dominant pathways of the reaction. Only a single isolated case of a cross-coupling has been reported.¹⁶³ It is only very recently that appropriate conditions have been discovered to couple selectively aryl Grignard reagents with alkyl halides possessing β-hydrogens under iron catalysis.¹⁶⁴ Nakamura described the use of FeCl₃ (5 mol %) in the presence of TMEDA

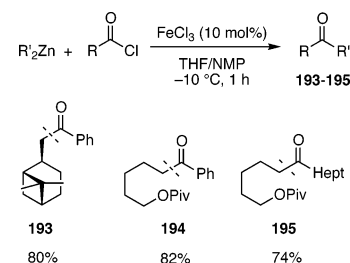
(1.2 equiv), and Hayashi and Nagano used Fe(acac)₃ in Et₂O for this purpose. The results are summarized in Table 10.

The conditions of Nakamura (method A) are generally more efficient than the ones of Hayashi (method B) and afford cross-coupling products in higher yields with various substrates and aryl Grignard reagents (up to 99%). However, the latter protocol is more attractive as the reaction is simply performed in refluxing Et₂O, without additive. Interestingly, Fe(acac)₃ was previously reported to be the best catalyst for cross-coupling of Grignard reagents with vinyl and aryl halides, but in THF/NMP as solvent (vide supra). So, according to the nature of the solvent, cross-couplings occur selectively with substrates such as **190** bearing both triflate and bromide substituents (Scheme 29).^{164b}

Scheme 29

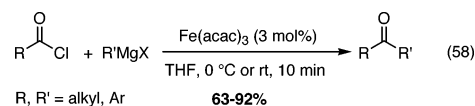


Scheme 30



3.3.4. Acyl Derivatives as Substrates

Reactions of acyl halides with organozinc¹⁶⁵ or Grignard¹⁶⁶ reagents in the presence of catalytic amounts of iron derivatives lead to ketones in good yields (Scheme 30 and eq 58, respectively). This latter reaction is compatible with functionalized aryl acyl chlorides,^{166b} and has been used in the preparation of 1,*n*-dicarbonyl compounds employing di-Grignard reagents.^{166c}



More recently, a supported analogue of Fe(acac)₃, made by polymerization of the 2-(acetatoacetoxy) ethyl metacrylate, has been used in the reaction.^{166d} The results are comparable to the ones obtained with the nonsupported catalyst.^{166d}

Thioesters **196** react with Grignard reagents in an analogous manner leading to the formation of corresponding ketone in good yield (eq 59).¹⁶⁷ This protocol

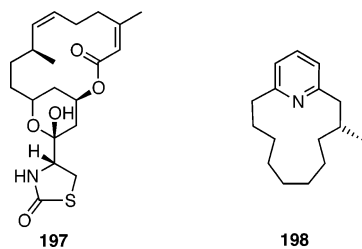


Figure 1.

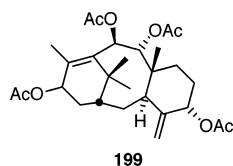


Figure 2.

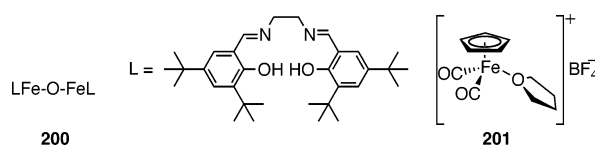
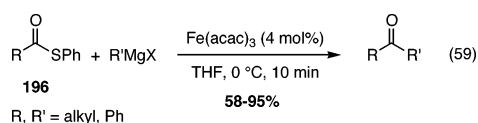


Figure 3.

found application in the total synthesis of (*Z*)-jasmone and dihydrojasmone.^{167d}



Various iron-catalyzed cross-coupling reactions have been successfully used by Fürstner in total syntheses of latrunculin B **197**¹⁶⁸ and (+)-muscovydine **198**¹⁶⁹ (Figure 1).

3.4. Conversions of Ethers into Acetates

Iron has also been used as catalyst for the conversion of ethers into acetates. In 1914, Knoevenagel observed the formation of ethyl acetate in the reaction of diethyl ether with ferric chloride in acetic anhydride.¹⁷⁰ This unusual reagent for the fragmentation of ethers and subsequent conversion to esters had largely been ignored by synthetic chemists until Ganem and Small evaluated the scope of this reaction (Table 11).¹⁷¹ With less than 35% of FeCl₃ in Ac₂O, ethers, including silyl ethers, are easily cleaved and alkyl moieties converted to the corresponding acetates in moderate to good yields (entries 1–3, 5, and 6). Benzyl ethers undergo Friedel–Crafts acylations (entry 3). With allyl and chiral ethers, the transformations can proceed with retention of configuration (entries 4, 6, and 7), but racemization has also been observed in some cases (entry 5). Furthermore, the transformation is compatible with functional groups such as cyano groups¹⁷² and chloro or carbonyl substituents (entries 4 and 7, respectively).

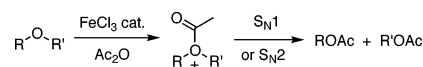
Ganem and Small proposed a dual mechanism involving *O*-acylation of the ether followed by disociation of the more stable carbonium ion or nucleophilic displacement at the oxonium ion by acetate (Scheme 31).¹⁷¹

Table 11. Iron-Catalyzed Cleavage of Ethers^a

entry	ether	FeCl ₃ (mol%)	temp. (°C)	time (h)	product [yield, (%)]
1	<i>n</i> -Butyl ether	20	80	16	<i>n</i> -Butyl acetate (45)
2	Isopropyl ether	15	80	24	Isopropyl acetate (83)
3	<i>n</i> -BuOBn	32	80	17	<i>n</i> -Butyl acetate (88) ^b
4		10	0	0.25	(83)
5		34	80	22	2-Octyl acetate (45) ^c Benzyl acetate (45)
6		15	0	0.25	(+)-2-Octyl acetate (45)
7 ^d		5	40	1	(80)

^a Ref 171. ^b No benzyl acetate was obtained. ^c Product was obtained as a racemate. ^d Reference 173a.

Scheme 31



This method has been successfully used in the prostaglandin chemistry,¹⁷³ the synthesis of pheromones,¹⁷⁴ and in the total synthesis of taxusin **199** (Figure 2).¹⁷⁵

It is worth noting that allylic and benzylic alcohols can undergo etherification with the same catalyst (or ferric perchlorate) in refluxing alcohol. The yields of the resulting ethers are often very high, although in some cases elimination products are obtained and the reaction is not stereoselective.¹⁷⁶

4. Cycloadditions

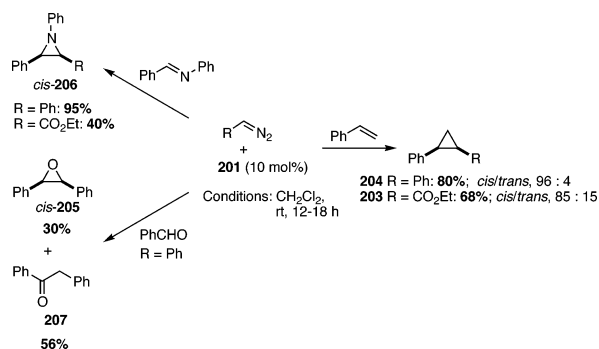
Cycloaddition reactions of unsaturated molecules are very powerful tools for the synthesis of cyclic products.¹⁷⁷ In this field, the use of transition metal catalysts can give very high selectivities under mild conditions.¹⁷⁸

4.1. [2+1]-Cycloadditions

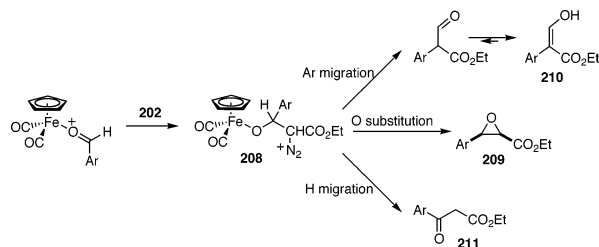
The reaction of diazo compounds with olefins, aldehydes, and imines is a common method for the synthesis of three-membered rings (cyclopropanes, epoxides, and aziridines, respectively). Some cyclopropanations involve iron-salen catalysts, and good results have been obtained with μ -oxo-bis[(salen)iron(III)] **200** (Figure 3 and eq 60).¹⁷⁹

The Fp cation, [CpFe(CO)₂]⁺, is a relatively mild Lewis acid, and the related complex [CpFe(CO)₂(THF)]⁺BF₄⁻ **201** (Figure 3) has been used as a catalyst for the synthesis of cyclopropanes. These

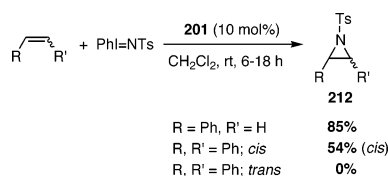
Scheme 32



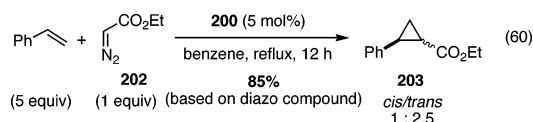
Scheme 33



Scheme 34



contributions originate from Hossain and co-workers, and a review has been recently published.¹⁸⁰



The reaction of phenyldiazomethane with olefins, aromatic aldehydes, and imines performed with 10 mol % of **201** affords the sterically more hindered cyclopropanes **204**,¹⁸¹ oxiranes **205**,¹⁸² and aziridines **206**¹⁸³ (*cis* selectivity), but satisfactory yields are only obtained for cyclopropanations and aziridinations. In the attempted epoxidation of benzaldehyde, ketone **207** was obtained as major product (Scheme 32).¹⁸²

The reactions with ethyl diazoacetate (**202**) catalyzed by **201** are more problematic. Only aromatic olefins react affording cyclopropanes in good yields and with high stereoselectivity (Scheme 32).¹⁸⁴ With aromatic aldehydes, the major products are not the expected epoxides **209** but β -hydroxy- α -arylacrylates **210** and β -ketoesters **211**, (Scheme 33).¹⁸⁵ The formation of these compounds is supposed to come from the unique intermediate **208** that rearranges depending of the nature of the diazo compound and the aryl group (Scheme 33).

Epoxide **209**, hydroxyacrylate **210**, and ketone **211** should be formed by *O*-substitution, 1,2 aryl migration, and H-migration, respectively.^{182,185} This route to acrylates, involving an unusual aryl migration, has been applied to the synthesis of a naproxen precursor.¹⁸⁶

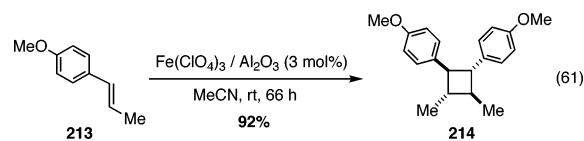
The reaction of ethyl diazoacetate with imines affords exclusively *cis* aziridines, but in low yields. Some β -amino- α,β -unsaturated esters are also obtained (10–40% yield).¹⁸³ Aziridines can also be synthesized starting from olefins and PhI=NTs as nitrenoid precursor (and limiting agent) using **201** as catalyst (Scheme 34).¹⁸⁷

The reactions provide aziridines with retention of configuration. Good yields are obtained when starting from monosubstituted alkenes, and moderate yields with *cis*-disubstituted ones. No reaction occurs with the *trans*-substituted olefins.¹⁸⁷

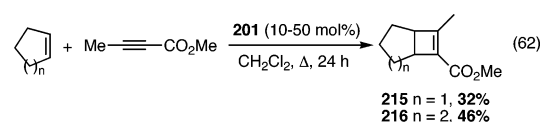
Polymer-¹⁸⁸ and silica-supported¹⁸⁹ analogues of catalyst **201** have also been synthesized and assessed. However, lower selectivities and yields are generally obtained.

4.2. [2+2]-Cycloadditions

The [2+2] cyclodimerization of *trans*-olefin **213** can be performed using $\text{Fe}(\text{ClO}_4)_3$ under air. Best results are obtained with a catalyst supported on aluminum oxide (3 mol %) affording exclusively the C_2 -symmetric cyclobutane **214** in 92% yield (eq 61).¹⁹⁰ Attempts to perform the reaction asymmetrically with chiral catalysts bearing BOX ligands remained unsuccessful ($ee_{\text{max}} = 7\%$), confirming the hypothesis of a radical cation pathway.

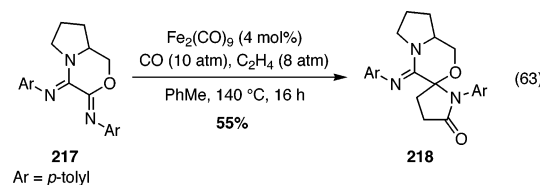


The reaction of cycloalkenes with methyl tetrolate catalyzed by **201** affords unsaturated bicycles, but only in low yields (eq 62).¹⁹¹



4.3. [2+2+1]-Cycloadditions

A single example of a hetero-Pauson-Khand-type [2+2+1] cycloaddition reaction of a ketimine, carbon monoxide, and ethylene has recently been reported by Imhof et al. (eq 63).¹⁹²

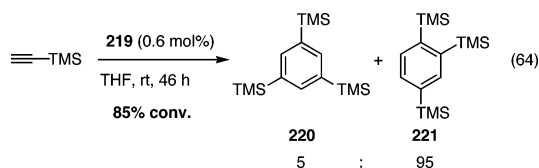


Only one of the two imine moieties is activated, and the reaction leads to the formation of pyrrolidinone derivatives **218** (55%).

4.4. [2+2+2]-Cycloadditions

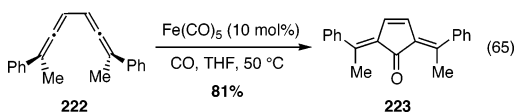
The cyclotrimerization and cyclocotrimerization of alkynes is catalyzed by iron(0) complexes, and leads to polysubstituted aromatic rings.¹⁹³ Good selectivity is obtained in the trimerization of trimethylsilylacetylene, with only 0.6 mol % of **219** $\{[\text{Fe}(\eta^6-$

cyclohepta-1,3,5-triene)(η^4 -cycloocta-1,5-diene)]} (eq 64).^{193a}



4.5. [4+1]-Cycloadditions

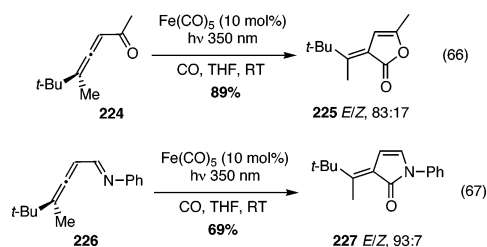
The assembly of five-membered carboxylic rings frequently involve [3+2] and Pauson-Khand [2+2+1] reactions. However, such cycles can also be obtained by [4+1] cycloadditions. In the early 90's, Eaton et al. reported the first example of a [4+1] reaction catalyzed by a transition metal-containing compound. In presence of $\text{Fe}(\text{CO})_5$ (10 mol %), carbon monoxide reacts with diallenes to give access to dialkyldenyrcyclopentenones (eq 65).¹⁹⁴



The stereoselectivity of the reaction indicates an initial " π -facial coordination" of the diallyne substrate **222** to the metal, followed by the formation of a metallocyclopentene intermediate and subsequent CO insertion.¹⁹⁴

Allenyl ketones (as well as aldehydes)¹⁹⁵ and allenyl imines¹⁹⁶ react with the same catalyst, under fluorescent light, to afford the corresponding alkylidenbutenolides and alkylidenpyrrolinones (Scheme 35).

Scheme 35



4.6. [4+2]-Cycloadditions

Iron-catalyzed Diels–Alder reactions between dienes and α,β -unsaturated carbonyl compounds as dienophiles have caught significant attention. Iron cyclopentadienyl complexes¹⁹⁷ and FeCl_3 adsorbed on silica¹⁹⁸ have been shown to be efficient for this purpose. More interesting is the use of chiral iron catalysts with C_2 -symmetric ligands to perform this [4+2]-cycloaddition in an asymmetric manner. The first example was reported by Corey et al. The reaction between 3-acryloyl-1,3-oxazolidin-2-one **228** and cyclopentadiene was catalyzed by an iron complex formed in situ from FeI_3 , I_2 , and chiral BOX ligand **230**.¹⁹⁹ The reaction affords predominantly the *endo* product **229** (92% selectivity, 95% yield) with 82% ee (Table 12, entry 1). Other C_2 -symmetric ligands such as bissulfoxide **231**²⁰⁰ and bisphosphine oxide **232**²⁰¹ (entries 2 and 3, respectively) have also

Table 12. Iron-Catalyzed Asymmetric Diels–Alder Reactions

entry	ligand	R	yield (%)	<i>endo/exo</i>	ee (%)
1		H	95	96:4	82
2		H	78	96:4	56
3 ^a		Me	85	42:58	<i>endo</i> , 72 <i>exo</i> , 74
4 ^b		H	90	99:1	98

^a In EtNO_2 at 0 °C. ^b With $\text{Fe}(\text{ClO}_4)_2$.

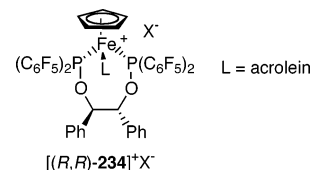


Figure 4.

been applied. However, the results obtained with such compounds are not as good as the previously reported ones, especially for the phosphine oxide ligand that affords the *endo* and *exo* products in a 2:3 ratio. The best results were achieved with $\text{Fe}(\text{ClO}_4)_2$ in combination with dibenzofurandiyl bis-oxazoline **233** (DBFOX). In this case, the *endo* Diels–Alder adduct **229** was obtained almost exclusively having 98% ee (entry 4).²⁰²

These examples indicate a very interesting future for iron-catalyzed asymmetric transformations, especially by using iron salts with noncoordinating anions such as perchlorate and iodide.

Another approach was introduced by Kündig et al., who developed iron cyclopentadienyl catalysts bearing chiral phosphites. The ligands had pentafluorophenyl rings at phosphorus and the C_2 -symmetric cores were derived from enantiopure *trans*-cyclopentandiol (CYCLOP-F), and subsequently from hydrobenzoin (BIPHOP-F; catalyst = **[234]⁺X⁻**).²⁰³

With 5 mol % of **[234]⁺BF₄⁻** (Figure 4), dienes react with acroleins to give the corresponding Diels–Alder adducts in very good yields. Furthermore, diastereoselectivities (generally *exo* products) are high and the enantioselectivities excellent (Table 13).

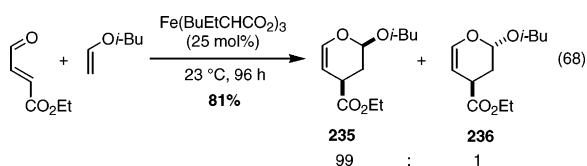
An example of a nonasymmetric hetero Diels–Alder reaction has also been reported. Among all iron carboxylate complexes assessed, iron(III) 2-ethylhexanoate was found to be the most efficient one (eq

Table 13. Asymmetric Diels–Alder Reactions Catalyzed by [234]⁺BF₄[−]

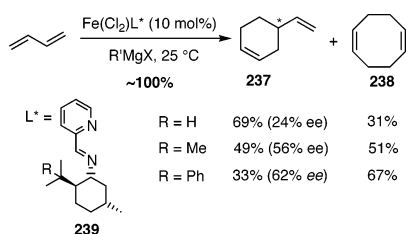
diene	dienophile	product	yield (%)	exo/endo	ee (%)
			69	98:2	97
			83	94:6	95
			90	only 1 regioisomer observed	98
			86	10:90	>99

^a Reactions performed with [234]⁺BF₄[−] (5 mol %) and 2,6-dimethylpyridine (5 mol %) in CH₂Cl₂ at −20 °C.

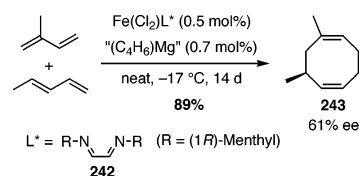
68).²⁰⁴ The reaction was highly diastereoselective (99:1) and afforded the product in good yield (81%).



The dimerization of dienes forms cyclic structures such as vinylcyclohexene (**237**) (by [4+2]-cycloaddition) and or cyclooctadiene (**238**) (by [4+4]-cycloaddition).²⁰⁵ With an iron(II) diazadiene (DAD) complex and an excess of Grignard reagent, butadiene assembles to give a mixture of the six- and eight-membered carbocycles. Depending on the nature of the ligand, the ratio between vinylcyclohexene and cyclooctadiene varies. The former product can be obtained with good enantioselectivity ($ee_{\max} = 62\%$ with **239**), when menthol-derived ligands on iron are applied (Scheme 36).²⁰⁵

Scheme 36

Cycloadditions of alkynes in the presence of conjugated dienes afford 1,4-hexadienes derivatives.²⁰⁶ This reaction is usually catalyzed by iron(0) catalysts. In an interesting example, the reaction of ynamines **240** in the presence of a large excess of butadiene and an in situ generated iron(0) complex afforded the

**Scheme 37**

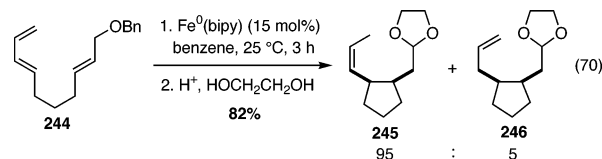
corresponding cyclohexadienamines **241** (>80% yield), which are precursors of cyclohexenones (eq 69).^{206a}

4.7. [4+4]-Cycloadditions

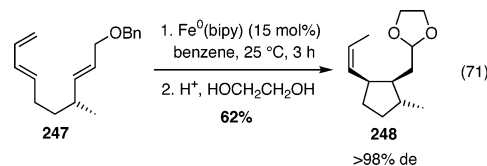
The codimerization of two different dienes can yield substituted cyclooctadienes. By using an iron complex with a chirally modified DAD ligand (**242**, 0.5 mol %) and in the presence of a butadiene magnesium-bis(tetrahydrofuran) complex, isoprene and *trans*-piperylene react to form selectively 1,7-dimethyl-1,5-cyclooctadiene (**243**) with 61% ee (Scheme 37).²⁰⁷

4.8. Ene Carbocyclization

Ene reactions²⁰⁸ of allylic ethers with dienes catalyzed by an iron(0)-bipyridine complex (generated from Fe(acac)₃/3 Et₃Al/bipy) have been extensively studied by Takacs et al.²⁰⁹ Mainly intramolecular versions were investigated.^{210–216} For example, carbocyclization of (*2E,7E*)-decatriene ether **244** afforded *cis*-cyclopentane derivatives **245** and **246** (in 82% overall yield), corresponding to a formal [4+4]- and a [4+2]-cycloaddition, respectively, in a ratio of 95:5 (eq 70).²¹⁰

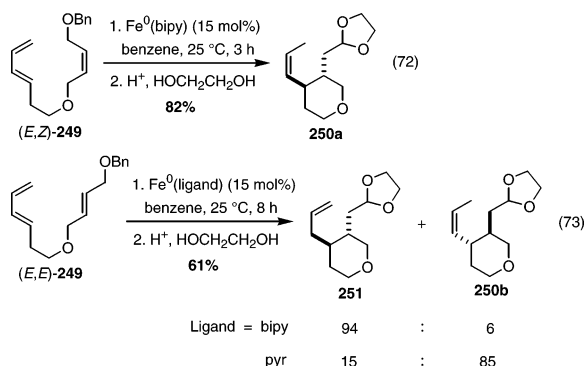


Interestingly, the chiral 4-methyl-substituted (*E,E*)-triene **247** undergoes iron-catalyzed [4+4] carbocyclization with excellent diastereoselectivity enabling control of the relative stereochemistry at three contiguous asymmetric centers. Thus, treatment of **247** with 15 mol % of bipy-Fe⁰ followed by acetalization yields a mixture of *cis*-cyclopentanes (62% overall) in which isomer **248** comprises greater than 98% (eq 71).²¹⁰



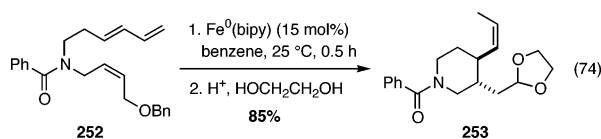
With (*E,Z*)-**249**, only the [4+4] reaction occurs, and a tetrahydropyran with *trans* configuration is obtained (**250a**, 82% yield). The other *trans* and *cis* isomers are present in less than 1% each (Scheme 38, eq 72).²¹¹ The selectivity of this reaction depends on the ligand and on the substrate configuration.²¹² When using the (*E,E*) isomer of **249**, a mixture of *trans* products resulting of [4+2] and [4+4] reactions are obtained with the former as major product (94:6). An inversion of the selectivity is observed, when

Scheme 38



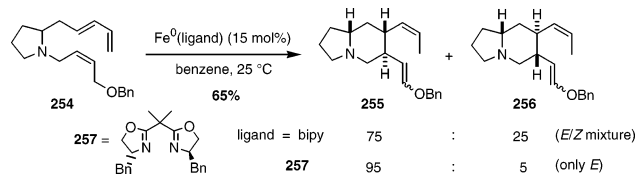
changing the ligand from bipyridine to pyridine and giving **251** and **250b** in a ratio of 15:85 (Scheme 38, eq 73).²¹¹

As interesting applications of this reaction, amide derivatives of piperidines **253** have been prepared in good yields and complete stereoselectivity (eq 74).²¹³



Access to heterobicycles has also been studied.²¹⁴ While an excess of ligand poisons the catalyst, it is rather surprising to note that amine-containing substrates undergo cyclizations.²¹⁴ Whereas compound **254** cyclizes to give indolizidines **255** and **256** in a 75:25 ratio (mixture of *E* and *Z* isomers) with bipyridine as ligand, the use of chiral BOX ligand **257** mainly affords **255** (in 95% yield as racemate) exclusively with *E* configuration at the enol ether double bond (Scheme 39).²¹⁴ Quinolizidines

Scheme 39



and oxobicycles can also be synthesized using similar processes.²¹⁴

This method has been successfully used as a key step in the enantioselective total synthesis of (–)-mitsugashiwalactone (**258**), (+)-isoiridomyrmecin (**259**),²¹⁵ and (–)-gibboside (**260**).²¹⁶ It has also been shown that triene ester **261** undergoes carbocycliza-

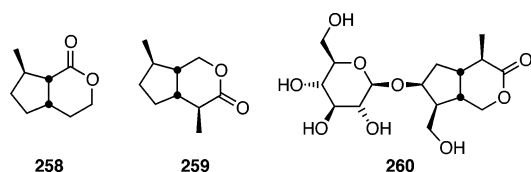
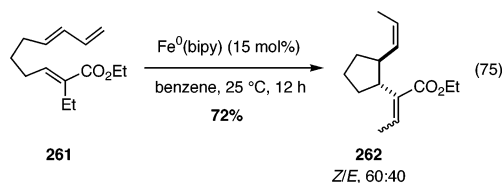
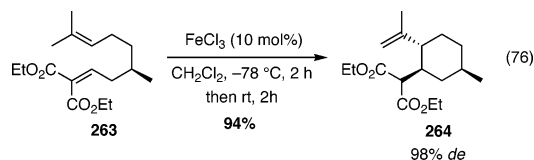


Figure 5.

tion under similar conditions to give **262** in 72% yield (eq 75).²¹⁷



Iron(III) chloride has been reported by Tietze and Beifuss to be a useful catalyst for intramolecular ene reactions. The diene Knoevenagel adduct **263** reacts with 10 mol % of FeCl_3 to give the corresponding six-membered ring **264** with 98% de in 94% yield (eq 76).²¹⁸



4.9. 1,3-Dipolar Cycloadditions

Kündig et al. used the iron chiral Lewis acid $[\mathbf{234}]^+\text{SbF}_6^-$ to catalyze 1,3-dipolar cycloaddition reactions between nitrones and enals. These reactions required 5 mol % of the catalyst and afforded the *endo* products with high enantioselectivity (up to 96% ee) and in good yields (Table 14).²¹⁹

Table 14. Enantioselective 1,3-Dipolar Cycloaddition Reactions Catalyzed by $[\mathbf{234}]^+\text{SbF}_6^-$

nitron	enal	product	yield (%)	ee (%)
			92	96
			71	96
			75	75
			71	94

This method gives access to isoxazolidines that are direct precursors of chiral 1,3-amino alcohols.

5. Hydrogenations and Reductions

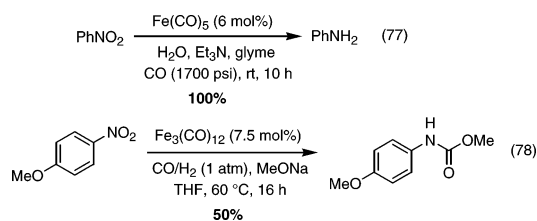
5.1. Hydrogenations

Hydrogenations of olefins,²²⁰ arenes,²²¹ imines,²²² ketones,²²³ and nitriles²²⁴ with iron catalysts (mainly iron carbonyls), under hydrogen atmosphere or water-gas shift conditions (WGS), i.e., CO , H_2O and base, have been investigated, but the harsh reaction conditions often required make these reactions generally unsuitable for the laboratory scale.

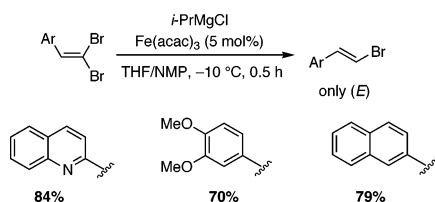
5.2. Reduction of Nitroarenes to Aniline Derivatives

Reduction of aromatic nitro compounds to amines has caught significant attention. When working

Scheme 40



Scheme 41

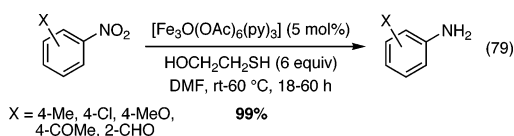


under WGS conditions, the reduction of nitrobenzene is complete and affords aniline in quantitative yield (Scheme 40, eq 77).²²⁵ In contrast, with hydrogen gas and MeONa as a base, the reaction mainly affords the corresponding aniline as the major product but as the corresponding carbamate (50%, Scheme 40, eq 78).²²⁶

The outcome of the second reaction is specific of iron catalysts and suggests the intervention of a species such as $[(\text{ArN})\text{Fe}_3(\text{CO})_9\text{COOCH}_3]^-$ that undergoes reductive elimination (and protonation) to afford the carbamate. Further mechanistic studies on the reduction of nitrobenzene to aniline by iron carbonyl catalysts have shown that a radical anion $[\text{Fe}_3(\text{CO})_{11}]^{\bullet-}$ was involved.²²⁷

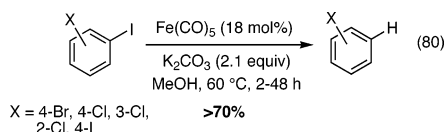
Other efficient processes for the reduction of nitro compounds have also been developed. Hydrazine²²⁸ or dimethyl hydrazine²²⁹ can be used for transfer hydrogenations with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (<2 mol %) and charcoal, in refluxing MeOH. For example, the reduction of 7-nitroindole gives the corresponding 7-aminoindole with dimethyl hydrazine in 90% yield.

The best results have been achieved with $[\text{Fe}_3\text{O}(\text{OAc})_6(\text{py})_3]$ (5 mol %) and 2-mercaptoethanol as reductant. A broad range of aromatic nitro compounds has been reduced to anilines with this system (eq 79).²³⁰



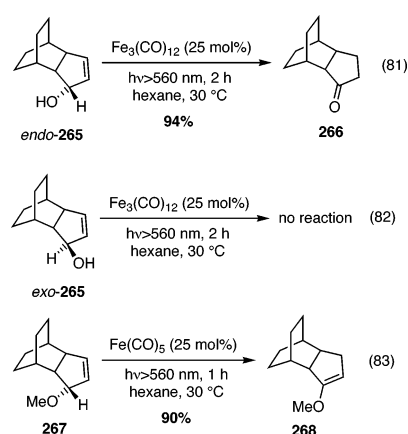
5.3. Reduction of Aryl and Alkenyl Halides

Iodo aryl compounds undergo selective hydrogenation under mild conditions with Fe(CO)_5 (18 mol %) and K_2CO_3 in methanol (eq 80).²³¹



The main feature of the reaction is its complete selectivity toward other halogenated positions. Even

Scheme 42



1,4-diiodobenzene is converted to iodobenzene (70% yield) and only minor amounts of benzene are formed.

During their investigations on Fe-catalyzed cross-couplings of vinyl halides with Grignard reagents (vide supra), Figadère and co-workers observed that 2-aryl-1,1-dibromo-1-alkenes undergo selective hydrodehalogenation under usual conditions to afford (E) vinyl bromides (Scheme 41).²³²

6. Isomerizations and Rearrangements

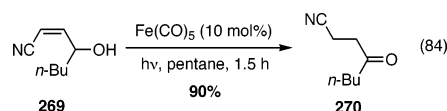
6.1. Double Bond Isomerizations

Iron carbonyl derivatives are active in the photocatalytic isomerization of alkenes, but these reactions are usually not selective and yield a mixture of olefins.²³³

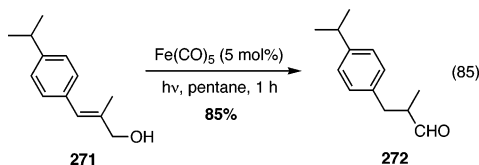
The conversion of allylic alcohols to saturated carbonyl compounds generally requires a two-step sequence of oxidation (reduction) followed by reduction (oxidation). The use of metal catalysts allows the reaction to be performed in a one-pot process and constitutes a more attractive strategy. It is an atom economic process, which may also minimize the number of protection–deprotection steps, which are often required. The complexes Fe(CO)_5 and $\text{Fe}_3(\text{CO})_{12}$ are the most versatile catalysts, and the reaction requires thermal or photoassistance. With 20 mol % of Fe(CO)_5 , cyclohex-2-en-1-ol affords cyclohexanone at 124 °C in 20% yield after 6 h. Under UV light, however, 3 mol % of the catalyst gives the same product in 40% yield after only 1 h.²³⁴

In some cases, the reaction occurs with a remarkable selectivity. For example, with allylic alcohol **265**, the *endo* isomer is easily converted to the corresponding ketone with 94% yield, while *exo-265* is totally unreactive. The same conditions can be applied to allylic ether **267**, which yields enol ether **268** (Scheme 42, eq 83).²³⁵

More recently, the isomerization of allylic alcohols has been applied to more functionalized compounds.²³⁶ The process is particularly efficient if the substrates have aryl or electron-withdrawing groups on the allylic systems (eq 84).



This methodology has been used in the synthesis of perfume components such as the cyclamen aldehyde **272** (eq 85).

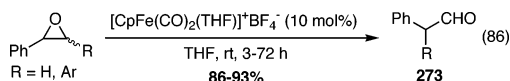


Allylamides have also been investigated as substrates. The corresponding enamides are obtained in good yields under similar conditions, but a low *cis/trans* selectivity is observed.²³⁷

It has been suggested that these isomerizations proceed through formation of a tetracarbonyl iron- π -complex and subsequent hydride shift, or that tricarbonyl iron is the active species giving hydrido- π -allyltricarbonyl iron as the intermediate.²³⁸

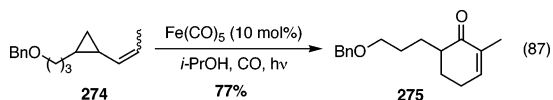
6.2. Ring Rearrangements

Iron complexes can also be used for the rearrangement of epoxides to give aldehydes. By using the cationic iron complex $[\text{CpFe}(\text{CO})_2(\text{THF})]^+\text{BF}_4^-$,¹⁸⁰ oxiranes are converted into aldehydes **273** as only products in high yields under mild conditions (eq 86).²³⁹

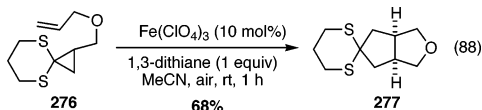


The mechanism of this reaction involves a carbocation formed by opening of the epoxide by the iron catalyst. Then, migration of an aryl group occurs to form the corresponding aldehyde.²³⁹

Cyclohexenones **275** are accessible by the rearrangement of vinyl cyclopropane **274** and CO insertion with $\text{Fe}(\text{CO})_5$, under CO atmosphere and irradiation (eq 87).²⁴⁰ The product is obtained in good yield (77%) and similar results can be obtained with only 5 mol % of the catalyst.

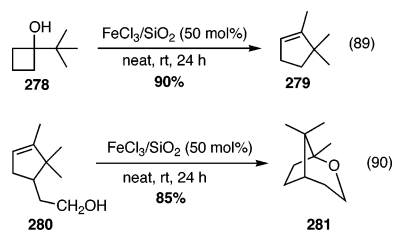


The expansion of a cyclopropyl ring with a dithioketal group proceeds in the presence of 10 mol % of iron(III) perchlorate under air atmosphere and with 1,3-dithiane (1 equiv) as reducing agent (eq 88).²⁴¹ The mechanism of this reaction is of radical-cationic nature and involves oxidation-reduction processes of the $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ couple to generate the radical species.²⁴¹



Enlargements of cyclobutane and cyclopentene derivatives bearing a hydroxy group can be easily performed with anhydrous iron trichloride absorbed

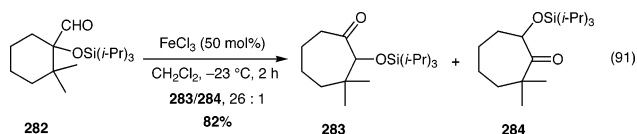
Scheme 43



on silica in substoichiometric amount (50 mol %) without solvent (Scheme 43).²⁴²

In both cases, the ring expansion occurs via a rearrangement of carbocationic species. For substrate **278**, this intermediate is formed by abstraction of the hydroxyl group of the substrate, while a proton transfer is responsible of the cation formation from **280**. The reactions lead to cyclopentene **279** and [3.2.1]oxabicyclooctane **281**, respectively, in high yields.²⁴²

The rearrangement of cyclic α -silyloxyaldehyde **282** can also be performed with an iron catalyst. The α -hydroxyketone produced by this ring extension is obtained in 82% yield (eq 91).²⁴³



The formation of the two α -hydroxyketones **283** and **284** reflects the two possible migration pathways. The most favored process is the migration of the more substituted carbon, which leads to the two products with a 26:1 ratio.

7. Polymerizations

The importance of polymerization reactions for almost all of the aspects of nowadays life is most obvious. A large number of common goods (including the computers used to write this paper) would not exist without the materials made available by polymerization processes.

The fact that small structural differences in the polymers can have a dramatic effect on their properties stimulated a vast research effort directed to gain control over these parameters. The use of metal complexes as catalysts for polymerization reactions,²⁴⁴ often following the indications of molecular modeling studies,²⁴⁵ furnished a key to this control. Among the different transition metals tested, iron has often given excellent results, from the point of view of both productivity and selectivity. This, together with its favorable characteristics of low price and toxicity (see Introduction), makes iron one of the most suitable metals for large-scale industrial applications.

7.1. Ethylene Polymerizations and Related Processes

Polyethylene and similar polyolefins are by far the most produced polymers in the world, representing a multibillion dollar *per* year industry, with world-

wide production in excess of 70 million tons in the mid 90's.^{246,247} It is therefore not surprising that tremendous effort has been made to develop metal-catalyzed versions of olefin polymerization reactions.²⁴⁸

The first application of an iron species as catalyst for this reaction was reported almost at the same time by Gibson²⁴⁹ and Brookhart²⁵⁰ in 1998. In both cases, the active species were generated from iron complexes bearing 2,6-bis(imino)pyridyl ligands (**285**), in which the imino nitrogens had bulky *ortho*-substituted aryl groups. Treatment of **285** with methylalumoxanes (MAO or MMAO) afforded the active catalysts, which showed a very high activity coupled with a remarkable selectivity, considering that, in contrast to catalyses with other metals, only linear polyethylene was obtained.²⁵⁰ It should also be noted that the results obtained with iron proved to be superior to those obtained with similar cobalt species under the same conditions.^{249,250}

Subsequent studies conducted by both groups^{251,252} revealed other striking aspects of the catalytic system in object. First of all, the nature of the substituents in the *ortho* positions of the aryl rings of the ligands has a decisive influence on the molecular weight of the product. When two bulky *ortho* substituents are present in **285**, long chain polyethylene is obtained. If the aryl rings bear only one bulky *ortho* substituent instead of two ($R^3 = R^4 = H$ in **285**), a dramatic falloff in the molecular weight of the resulting polyethylene is observed, thus allowing the selective production of ethylene oligomers ($M_w = 260\text{--}470\text{ g}\cdot\text{mol}^{-1}$). The catalytic activity, however, remains exceptionally high, with reported turnover frequencies up to $1.8 \times 10^8\text{ h}^{-1}$,²⁵¹ again accompanied by complete selectivity toward linear compounds. These results are among the best ever reported for ethylene oligomerization processes.

Interestingly, if the *ortho* positions bear only small alkyl groups (i.e., methyl or ethyl), or no substituent at all, the system can be used to perform head-to-head dimerization of α -olefins, the linear products being once again preferred.²⁵³

The molecular weight of the produced polymer also depends on the Al/Fe ratio and the ethylene pressure. Oligomers are formed when the latter is increased.²⁵² In addition, two different termination pathways, β -H transfer (to monomer or metal) and chain transfer to aluminum, have been identified for the process.²⁵² The ratio between the rates of them is influenced by both the structure of the catalyst and the reaction conditions, allowing the resulting chain length distribution to be systematically altered.²⁵²

As a consequence of its unique features, this system has been the subject of detailed theoretical studies, directed both to establish the structure of the actual catalyst,²⁵⁴ and to clarify some mechanistic aspects of the process.²⁵⁵ Unfortunately, despite these investigations, the mechanism of the reaction remains in part still unclear. Recently, Gibson and co-workers introduced a modification of the bis(imino)pyridyl ligands by changing the aryl rings to amino and heterocyclic moieties. The resulting structures then possess two N–N bonds as shown for **286**.²⁵⁶ The

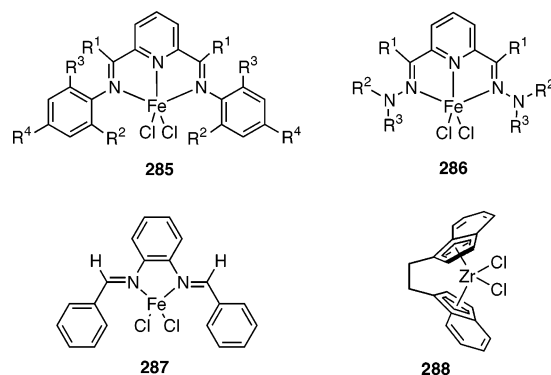


Figure 6.

catalysts resulting from the activation of the corresponding iron(II) complexes with MAO proved to be active in ethylene polymerization, even if the results were not comparable with those obtained employing the previously described system.

Further variations, such as the use of ammonium [tetrakis(pentafluorophenoxy)borate] as cocatalyst instead of the usual aluminum species,²⁵⁷ and employment of diimine iron(II) complexes (such as **287**) together with ethylalumoxane (EAO),²⁵⁸ have been described, but once again the results originally reported remain unmatched.

Finally, an isolated example of a tandem catalytic system based on iron and zirconium is present in the literature.²⁵⁹ By combining the action of an iron complex of type **A** (**285** with $R^1 = \text{Me}$, $R^2 = \text{Et}$, $R^3 = R^4 = \text{H}$) with the one of a Britzinger-type zirconium complex (**288**), the selective production of branched polyethylene in the presence of ethylene as the only monomer feed has been achieved. This allowed avoiding the use of superior olefins as comonomers, thus improving the efficiency of the process.

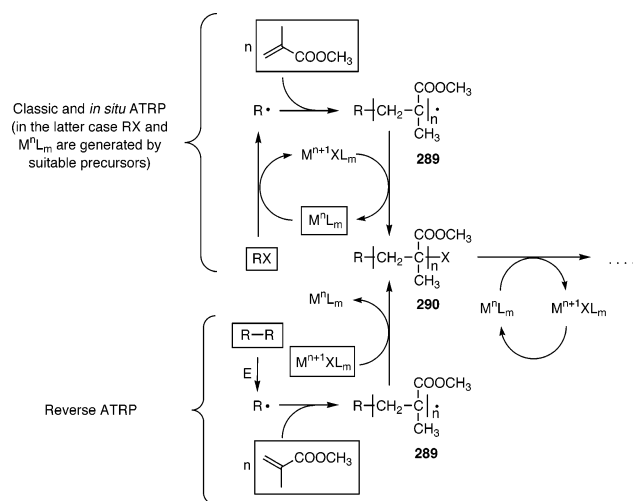
7.2. Olefin Polymerizations via ATRP Reactions

Atom transfer radical polymerization (ATRP) is today one of the most effective protocols available to achieve controlled/"living" radical polymerizations of a range of monomers, and it is used in the mass production of various materials such as polystyrene and polyacrylates.²⁶⁰ Three different classes of ATRP processes are known to date and are depicted in Scheme 44, where methyl metacrylate (MMA) is taken as the monomer.

In "classic" ATRP reactions, organic halides are used as initiators, transition metal compounds in their lower oxidation state (M^nL_m) are used as catalysts, and electron-donating compounds are used as ligands. The initiation step takes place by transfer of a halogen atom from the organohalide RX to the catalyst. The resulting radicals $R\bullet$ can then add one or more monomer units before reacting with the oxidized form of the catalyst, leading to a dormant chain. The repetition of this process produces high polymer chains.

In reverse ATRP reactions, a radical initiator and a higher oxidation state transition metal catalyst complex ($M^{n+1}XL_m$) are used. The initiation step now consists simply of the decomposition of the radical initiator. The situation becomes then exactly the

Scheme 44



same as in classical ATRP. This alternative protocol allows circumventing the two common drawbacks of the classic process: the use of halide species RX , which often are toxic or not easy to handle, and the possible oxidation of the catalyst by oxygen from air.

In the third class of ATRP processes, namely, “*in situ* ATRP”, RX and M^nL_m are generated *in situ* from the reaction between a radical initiator and a metal salt. Also in this case, the polymerization then proceeds through the conventional ATRP pathway.

Iron species have first been introduced as catalysts for ATRP reactions in 1997, independently by Sawamoto²⁶¹ and Matyjaszewski.²⁶² Initially, they were used in the “classic” protocol, but subsequently they have also been utilized in reverse and *in situ* ATRPs.

According to the first reports,^{261,262} various iron(II) complexes, prepared starting from $FeCl_2$ or $FeBr_2$ with triphenylphosphine,^{261,262} trialkylamines, and substituted bipyridines²⁶² as ligands, proved to be active catalysts for the controlled polymerization of styrene and MMA.

The molecular weight of the polymer was found to increase with monomer conversion, the molecular weight distributions (polydispersities) were rather narrow, and the tacticity of the polymer was similar to those obtained in AIBN-initiated processes. These observations were all consistent with a living radical polymerization. Further mechanistic evidence was revealed when a fresh feed of monomer was added in the reactor after the first charge was almost consumed and when it actually polymerized.²⁶¹

The first iron-catalyzed reverse ATRP process was described a year later.²⁶³ In this case AIBN was used as radical initiator, and $FeCl_3$ was the catalyst with triphenylphosphine as ligand. The results obtained for the polymerization of MMA resembled those of Sawamoto and Matyjaszewski, the rate of the reaction being even greater. Almost full conversion of the monomer was achieved within 2 h for the bulk polymerization at 85 °C.

An *in situ* process was reported for the first time in 2000 by Chen and Qiu,²⁶⁴ who used an initiating system consisting of tetraethylthiuram disulfide (TD), $FeCl_3$, and triphenylphosphine for the polymerization of MMA. Although the molecular weight of the

produced PMMA was lower than in previous reports, the reaction showed an astonishing rate, with 85% conversion of the monomer within less than 10 min at 100 °C. The polydispersity index was furthermore very narrow (<1.1), indicating an almost perfect control on the chain length of the product. Later, the same authors reported a halide-free initiating system in which TD was replaced by the iron complex $Fe(dtc)_3$.²⁶⁵ This time, both efficiency and selectivity were comparable to the previous ones.

Following these first studies, several modifications appeared later in the literature, aiming at both improving the efficiency of the reaction and minimizing some of its major drawbacks.

Thus, half metallocene iron(II) carbonyl complexes were found to be active catalysts for the ATRP of styrene,²⁶⁶ and also dinuclear iron(I) species such as $Fe_2Cp_2(CO)_4$ were employed to promote the reaction.^{266b} In this latter case, the polymerization was even faster, although slightly higher polydispersities were obtained. Cyclic voltammetry studies suggested that the improved reaction rate could be due to the lower redox potential of iron(I) complexes in comparison to iron(II) half metallocenes, which facilitated the oxidation of the metal in the initiation step (cf. Scheme 44).^{266b}

The same catalytic system has been used in the attempted polymerizations of para-substituted styrenes and the block copolymerization of styrene and MMA. In any case results strongly depended on the nature of the monomers.²⁶⁷ In a very interesting approach, use of iodinated sucrose, glucose, and cyclodextrin initiator cores in the same reaction allowed obtaining polystyrene stars with 5, 8, and 18 arms, respectively.²⁶⁸

Halide anions have also been applied as ligands using tetraalkylammonium species as counterions. Unfortunately, satisfactory results were obtained only using the “classic” ATRP protocol.²⁶⁹ Grubbs reported that iron(II) halides possessing highly donating imidazolyldene ligands were valuable catalysts for this reaction. The reaction rates of up to $3.4 \times 10^{-5} s^{-1}$ are among the highest ever reported for metal-catalyzed ATRP in organic solvents.²⁷⁰

Very recently, it was found that also iron(II) complexes with tridentate salicylaldiminato ligands were able to promote the ATRP reaction. Once again, the results obtained were outstanding. This time, well-controlled and very fast radical polymerizations of styrene were achieved through the reverse protocol.²⁷¹ The authors suggested that a reason for the exceptional behavior of these complexes could be found in the rigidity of the salicylaldiminato ligand. Further studies are expected to reveal if this is a general effect, and therefore an important feature for the design of novel ATRP catalysts.

7.3. Other Polymerizations

Apart from ethylene poly- and oligomerization and ATRP processes, iron species have also been shown to catalyze other polymerization reactions, even if only isolated reports can be found, and systematic studies such as those presented in the previous paragraphs are not yet available.

Iron-arene complexes were used in the technologically important field of photopolymers production, in particular, as initiators for the photo cross-linking of epoxides.²⁷²

Monocarboxylic iron(II) derivatives (acetate, butyrate, isobutyrate, and trifluoroacetate) have been utilized to promote the ring opening polymerization of L-lactide, to yield valuable aliphatic polyesters.²⁷³ With a catalyst loading ranging from 0.12 to 1.2% a monomer conversion over 85% was obtained under optimal conditions, leading to poly(L-lactide) with a molar mass of ca. 150 000 g·mol⁻¹. Unfortunately, partial racemization of the polymerization products was observed.

As previously indicated (cf. paragraph 2.2, eq 9), an iron-catalyzed poly-Michael addition was reported by Christoffers et al. in 2000.³⁸ The high efficiency of the process, together with the suppression of all the possible side reactions, allowed obtaining the product in high yield.

Two interesting processes for the polymerization of aniline have been published, which use an iron(II) or iron(III) species as catalyst and hydrogen peroxide or ozone as stoichiometric oxidant.^{274,275} In the latter case,²⁷⁵ iron(III) is able to oxidize aniline through a single-electron transfer to give aniline radical cations. While the latter react with aniline to form dimers, oligomers and finally polyaniline through multistep reactions, the iron(II) ions produced are reoxidized to iron(III) by ozone, thus being able to continue the reaction.

Finally, a sole example of an iron-catalyzed radical polymerization of MMA in water emulsion has been reported.²⁷⁶ Iron(II) chloride was the catalyst in this case, while various bisulfites were used as initiators and dodecyl benzene sulfonate was the emulsifier.

8. Miscellaneous

8.1. Sulfide Oxidations

Selective oxidations of sulfides to sulfoxides with iron catalysts and H₅IO₆²⁷⁷ or HNO₃²⁷⁸ as oxidants have been reported, and they offer interesting alternatives to existing methods.²⁷⁹ However, to effect this reaction with iron catalysts in an asymmetric fashion has always been a major challenge. Whereas the field is largely dominated by applications of titanium, manganese, and vanadium complexes, iron is relatively underrepresented, and the few systems developed so far fail in terms of efficiency and practicality.²⁸⁰ Most involve structurally complex iron porphyrins and iodosylbenzene as terminal oxidant, and the enantioselectivities are only moderate (<55% ee).²⁸¹ For example, complex **291** has been reported by Fontecave and co-workers to catalyze sulfide oxidations with H₂O₂, but the enantioselectivity remained rather low (e_{max} = 40%).²⁸² It is only very recently that a major breakthrough has been achieved. Legros and Bolm reported a highly enantioselective iron-catalyzed asymmetric sulfide oxidation, which provides optically active sulfoxides with up to 96% ee in good yield under very simple reaction conditions (Table 15).²⁸³

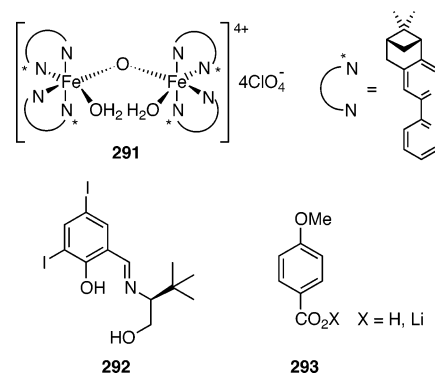


Figure 7.

Table 15. Iron-Catalyzed Asymmetric Sulfide Oxidation with H₂O₂ as Terminal Oxidant

$$\text{R-S-R}' \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt, 16 h}]{\begin{array}{c} [\text{Fe}(\text{acac})_3] / \text{ligand } \mathbf{292} / \mathbf{293} \\ (2 : 4 : 1 \text{ mol}\%) \\ 30\text{-}35\% \text{ aq. H}_2\text{O}_2 (1.2 \text{ equiv}) \end{array}} \text{R-S(=O)-R}'$$

entry	sulfide	product	
		yield (%)	ee (%)
1	Ph-S-Me	63	90
2	Ph-S-Et	56	82
3	Ph-S-CH ₂ Ph	73	79
4	Ph-S-CH ₂ -CH=CH ₂	63	71
5	4-Me-C ₆ H ₄ -S-Me	78	92
6	4-Br-C ₆ H ₄ -S-Me	59	94
7	4-Cl-C ₆ H ₄ -S-Me	60	92
8	4-NO ₂ -C ₆ H ₄ -S-Me	36	96
9	2-Naphthyl-S-Me	67	95

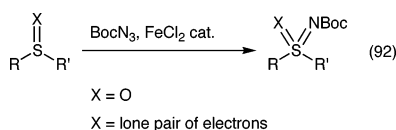
The best results have been obtained in the oxidation of aryl methyl sulfides (ee >90%, entries 1, 5–9). Remarkable enantioselectivities have also been achieved with more challenging substrates such as phenyl ethyl- and phenyl benzyl sulfides, which gave the corresponding sulfoxides with 82 and 79% ee, respectively (entries 2 and 3). Interestingly, the reaction is chemoselective since in phenyl allyl sulfide only the sulfur atom is oxidized, while the double bond remains unchanged during the reaction course (entry 4).²⁸⁴ This methodology has been applied to the asymmetric synthesis of sulindac (>90% ee), a biologically active chiral sulfoxide.²⁸⁵

The advantages of this process are the following: (1) the oxidation can be performed without particular precautions as the presence of water and air does not affect the outcome. (2) Simple aqueous hydrogen peroxide (35%, 1.2 equiv) is the most efficient oxidizing agent. (3) [Fe(acac)₃] is commercially available and inexpensive. (4) Ligand **292** is easily prepared from *tert*-leucinol and the corresponding salicylaldehyde derivative. (5) The presence of 1 mol % of 4-methoxybenzoic acid (**293**) or its carboxylate lithium salt greatly improves the efficiency of the reaction.^{283b} Without this additive yields of sulfoxides did not exceed 44%, and only one single sulfoxide could be obtained with more than 80% ee.^{283a} Whereas no evidence on the nature of the catalytic species is yet provided, the intervention of a diiron species with a bridging monocarboxylate similar to those investigated in MMO mimics has been suggested on the basis of the observed asymmetric amplification.²⁸⁴ The simplicity of the protocol and the high enanti-

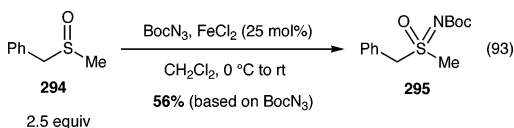
oselectivities render this process an attractive alternative to the currently existing methods for metal-catalyzed asymmetric sulfide oxidations.

8.2. Synthesis of Sulfoximides and Sulfinimides

The transfer of a nitrene fragment to sulfur compounds leads to the corresponding *N*-substituted sulfimides. Bach and Körber reported that FeCl₂ could be used with *tert*-butyloxycarbonyl azide (BocN₃) for nitrene transfer to sulfoxides and sulfides, affording sulfoximides and sulfimides (eq 92).²⁸⁶

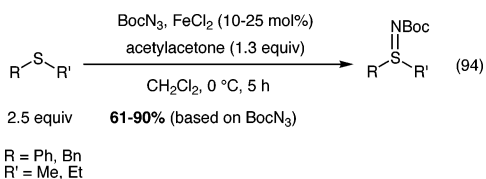


Whereas generally 1 equiv of iron(II) chloride was applied in the imidation of sulfoxides, satisfactory yields could also be obtained with 25–50 mol % of the catalyst (eq 93).



The reaction proceeds stereospecifically. Thus, when using enantiomerically enriched sulfoxides, the reaction delivers the corresponding sulfoximides without deterioration of the ee. The free NH-sulfoximine is then easily obtained after Boc cleavage. Bolm and co-workers used this reaction in the synthesis of sulfoximines having a benchrotene skeleton.²⁸⁷ This process is interesting as chiral sulfoximines are efficient auxiliaries in asymmetric synthesis, and a promising class of chiral ligands, which can be applied in various enantioselective catalyses.²⁸⁸

The imidation of sulfides is easier and sulfimides are obtained in moderate to good yields, especially when acetylacetone or DMF is added as ligand or cosolvent, respectively (eq 94).



A reaction mechanism is proposed that suggests the intermediacy of an *N*-Boc substituted Fe(IV)-nitrene complex [(Cl)₂Fe^{IV} = NBoc] acting as the imidation reagent in the catalytic cycle.

8.3. Nitrene and Carbene Transfer Reactions to Allyl- and Propargyl Sulfides

Allyl aryl sulfides undergo an imidation/[2,3]-sigmatropic rearrangement sequence when submitted to the BocN₃/FeCl₂ reagent combination yielding *N*-allylamines protected by a Boc and a phenylsulfanyl group in good yields (Scheme 45 and Table 16).²⁸⁹

Scheme 45

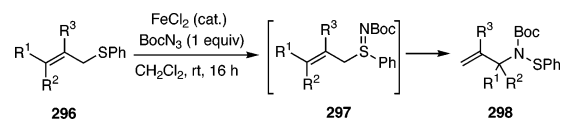
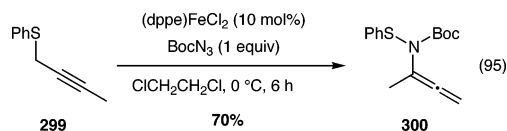


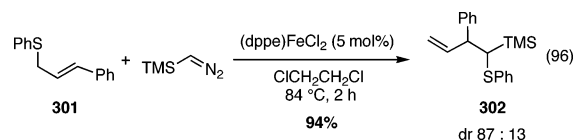
Table 16. Synthesis of Protected *N*-allyl Sulfenamides According to Scheme 45

R ¹	R ²	R ³	FeCl ₂ (mol %)	yield (%)
H	CH ₂ OH	H	25	70
H	<i>i</i> -Pr	Me	25	70
Me	Me	H	10	66

The phenylsulfanyl group is easily removed using Bu₃SnH/AIBN or P(OEt)₃/Et₃N affording the *N*-Boc protected *N*-allylamines. It should be noted that, whereas the imidation/rearrangement sequence is well suited for the transformation of α-unbranched sulfides to α-branched sulfenamides, enantiomerically pure α-branched sulfides react sluggishly and the products are obtained with low ee. Van Vranken et al. recently showed that propargyl sulfides are also efficient reaction partners in this transformation affording *N*-allenylsulfenimides upon treatment with (dppe)FeCl₂ (eq 95).²⁹⁰

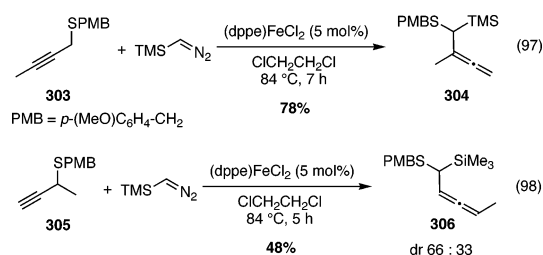


A [2,3]-sigmatropic rearrangement also occurs when allyl sulfides are reacted with (trimethylsilyl)diazomethane in the presence of the latter catalyst and, in this case, a new C–C bond is formed.²⁹¹ This reaction was formerly known with rhodium, cobalt, and copper catalysts (Doyle-Kirmse reaction).²⁹² With 5 mol % of the iron catalyst, the reaction is complete within 2 h and excellent yield and good stereoselectivity of the α,β-branched homoallyl sulfides are obtained (eq 96).



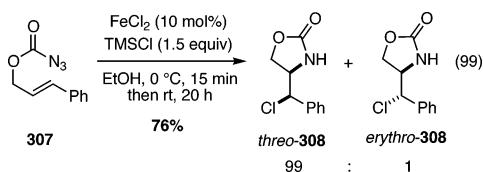
Several iron catalysts have been assessed. Either iron(II) or iron(III) complexes (FeBr₂, FeCl₃) can be used, and good yields are also obtained without phosphine ligand. However, as iron salts are hygroscopic and have poor solubility in chlorinated solvents, the use of a phosphine ligand circumvents these drawbacks. Unlike reactions with more traditional metal catalysts, reactions with iron salts give good yields without slow addition of the diazo compound or a large excess of reagents. Propargyl sulfides can also be used as substrates and afford allenyl α-silyl sulfides (48–90% yields).²⁹³ Various propargyl sulfides, either mono- or disubstituted, react in this reaction (Scheme 46). However, with chiral substrates the reaction proceeds with only low diastereocontrol (eq 98).

Scheme 46



8.4. Intramolecular Aminochlorination of Alkenes and Alkynes

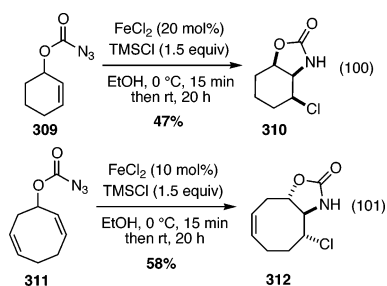
With iron(II) chloride and TMSCl alkenyloxycarbonyl azides undergo an intramolecular iron-catalyzed aminochlorination, which furnishes the corresponding chloromethylloxazolidinones (eq 99).²⁹⁴ With **307**, the reaction gives only the *threo* product **308** in good yield (76%).



Substrates of this type are known to undergo an intramolecular aziridination under thermal conditions, and the strained aziridines formed thereby are easily opened by nucleophiles. When the reaction is performed with **307** in refluxing trichloroethane (without catalyst and TMSCl), only *erythro*-**308** is afforded (trichloroethane is the source of chloride ions). The absence of any aziridine intermediate detected with the FeCl₂/TMSCl combination and the observed stereoselectivity are in line with an iron(II)-catalyzed nitrogen transfer *via* radical intermediates.

Cycloalkenoxycarbonyl azides also react and the stereoselectivity is dependent on the ring size (Scheme 47). With cyclohexene derivative **309** a *cis*

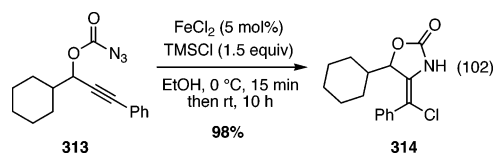
Scheme 47



insertion occurs (eq 100). In contrast, only a *trans* insertion is observed with cyclooctadienyl substrate **311** (eq 101).

The difference in the stereoselectivity can be explained by the different conformations of the six- and the eight-membered rings and a change in the iron coordination to the heteroatoms during the nitrene insertion and chlorine transfer.^{294b}

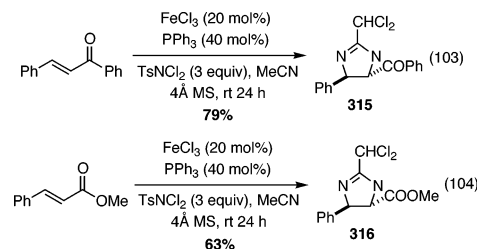
Under similar conditions, propargyloxycarbonyl azide **313** undergoes selectively a *syn*-aminochlorination (eq 102).²⁹⁵



8.5. Alkene Diaminations

The FeCl₃-PPh₃ complex promotes the electrophilic diamination reaction of α,β -unsaturated carboxylic esters and ketones (Scheme 48). The reaction

Scheme 48



employs readily available TsNCl₂ and acetonitrile as nitrogen sources and leads to imidazolidines **315** and **316** in good yields and with high regio- and stereoselectivity (*trans*).

The reaction is suggested to involve an aziridinium intermediate, which is further attacked by acetonitrile to give a nitrilium intermediate. The opening of the aziridinium ring by MeCN occurring on the β -position is responsible for the complete regiochemical control.

8.6. Allylic Aminations

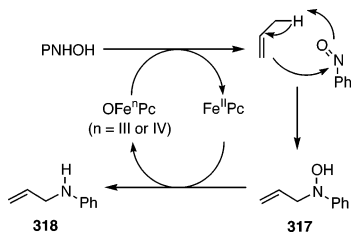
The addition of nitrogen derivatives to unsaturated systems is an interesting way to obtain allylamine fragments.²⁹⁶ The iron-catalyzed allylic amination of double bonds with phenylhydroxylamine has been independently reported by Jørgensen²⁹⁷ and Nicholas²⁹⁸ in 1994. In the presence of an iron phthalocyanine complex (FePc; method A),²⁹⁷ or a 9:1 mixture of FeCl₂·4H₂O/FeCl₃·6H₂O (method B),²⁹⁸ olefins react with PhNHOH in a formal hetero-ene process to give the corresponding allylamines in low to moderate yields (Table 17).²⁹⁷

With FePc, the reaction is limited to olefins conjugated with an aromatic ring, and the best yield is obtained with α -methylstyrene as substrate (entry 1). Conversely, the use of the Fe^{II}/Fe^{III} catalyst is more efficient with nonterminal acyclic olefins (entries 7 and 8). In the case of the latter catalyst, substrate scope and efficiency are greatly increased when PhNHOH is substituted by 2,4-dinitrophenylhydroxylamine (up to 75% yield).²⁹⁹ The poor results often observed with both catalysts can be explained by the decomposition of phenylhydroxylamine into

Table 17. Iron-Catalyzed Allylic Aminations of Olefins with PhNHOH

entry	substrate	method ^a	product	yield (%) ^b
1		A		76
2		B		31
3		A		62
4		A		45
5		A		30
6		B		9
7		B		65
8		B		47

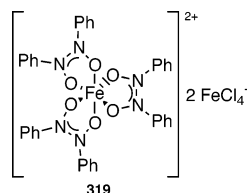
^a Method A: Reaction performed with FePc (5 mol %), olefin (5 equiv), and PhNHOH (1 equiv) in toluene under reflux for 10 h. Method B: Reaction performed with FeCl₂·4H₂O/FeCl₃·6H₂O (9:1, 10 mol %), olefin (1 equiv), and PhNHOH (2 equiv) in dioxane at 80 °C. ^b GC yield.

Scheme 49

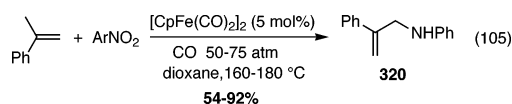
aniline, azobenzene, and azoxybenzene in the presence of iron complexes.³⁰⁰

Two different mechanisms have been suggested depending on the nature of the iron complex. With FePc, the -NR transfer occurs “off” the metal, and the role of the iron complex is to form nitrosobenzene from phenylhydroxylamine. Furthermore, the catalyst plays a crucial role in the formation of allylic amine **318** from hydroxylamine **317**, which is formed by a hetero-ene reaction of PhNO with the alkene (Scheme 49).³⁰¹

Conversely, Nicholas et al. have shown that the reaction catalyzed by iron chloride salts does not involve a free PhNO intermediate, but an azo dioxide complex **319** (Figure 8).³⁰²

**Figure 8.**

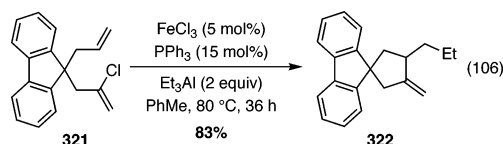
Nitroarenes can also be used as aminating agents. The reaction is then performed with [CpFe(CO)₂]₂ (5 mol %) under carbon monoxide pressure (eq 105).³⁰³



For the allylation of styrene with nitroaryl compounds bearing electron-withdrawing substituents this iron catalysis is very efficient. The high temperature and pressure can be reduced when the reaction is photoassisted.³⁰⁴

8.7. Cyclizations of Chlorodienes

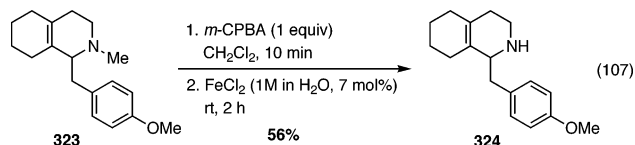
Recently, Kotora et al. reported the transformation of 2-chloro- α,ω -diene **321** with FeCl₃/PPh₃ and triethyl aluminum giving spiro-cyclic product **322** in 83% yield (eq 106).³⁰⁵



While the authors expected to perform an “iron-catalyzed Heck reaction”, the substrate underwent an alternative cyclization accompanied by an ethyl transfer from Et₃Al. Unfortunately, only very few substrates underwent this transformation, and the mechanistic pathway is still unclear.

8.8. Dealkylations of Tertiary Amine Oxides

The dealkylation of tertiary amine oxides upon treatment with acid anhydrides (Polonovsky reaction) has been successfully applied by Potier and co-workers as key reaction step in the preparation of antitumor alkaloids.³⁰⁶ Secondary amines can also be generated by dealkylative reduction of tertiary amine oxides with iron salts (eq 107).³⁰⁷



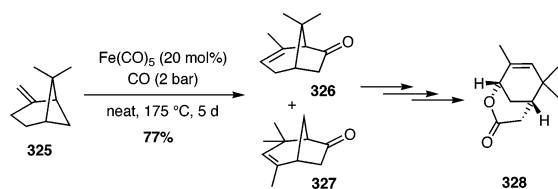
The reaction proceeds under mild conditions, and it is compatible with a variety of functional groups (ketone, aniline, allylamine, alcohol).

8.9. CO Insertions

On the basis of a known pentacarbonyliron-mediated CO-insertion,³⁰⁸ Blechert developed a catalytic version and used it as key step in the synthesis of enantiomerically pure taxoidic A,B-ring fragments (Scheme 50).³⁰⁹

With Fe(CO)₅ (20 mol %) and 2 bar of CO (–)- β -pinene (**325**) was transformed, on a 80 g scale, into a 1:1 mixture of isomeric ketones **326** and **327**. Despite the harsh conditions (175 °C, without solvent, 5 days) good yields were achieved. The low selectivity of the CO insertion was compensated by developing

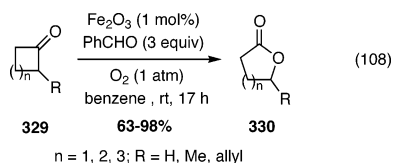
Scheme 50



two convergent synthetic pathways leading to lactone **328**, which is a common precursor of the target molecule.

8.10. Baeyer–Villiger Reactions

An iron-catalyzed Baeyer–Villiger reaction has been reported by Murahashi et al.³¹⁰ They found that Fe_2O_3 can efficiently promote the aerobic oxidation of several cycloalkyl ketones **329** to the corresponding lactones **330**, in the presence of an aldehyde (excess) as co-reductant (eq 108).



The iron catalyst is supposed to play a crucial role in the oxidation of the aldehyde with molecular oxygen, generating an oxidizing species, which is able to promote the transformation of the substrate to a lactone. Other salts than Fe_2O_3 proved to be ineffective, and the reaction showed a remarkable solvent effect, with benzene being by far the most effective medium.

9. Conclusions

This review compiled the applications of iron catalysts (less than 50 mol %) in organic synthesis. Whereas for decades only a few iron-catalyzed C–C bond formation reactions have been developed, the field now comprises many major accomplishments, and efficient processes for addition, cross-coupling, and cycloadditions reactions have emerged over the last 10 years. Significant progress has also been made in enantioselective transformations as exemplified by the achievements in Diels–Alder reactions, 1,3-dipolar cycloadditions and sulfoxidations. While the number of reactions is still limited, these results constitute the basis of a promising new area of research. The numerous advantages of this metal make it highly attractive, especially for large-scale applications, and iron catalysts will surely become an even more powerful tool for organic synthesis in the forthcoming years.

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11. Note Added in Proof

As confirmations of the vitality of the research concerning iron-catalyzed organic reactions, several studies appeared after the submission of the present review. Ghosez reported an FeCl_3 -catalyzed acetalene reaction,³¹¹ and Chaudhari showed that iron salts promote the hydrogenation of substituted nitroarenes.³¹² An $\text{Fe}(\text{acac})_3$ -catalyzed cross-coupling reaction between aroyl cyanides and Grignard reagents was published by Knochel,³¹³ while in three different papers Fürstner addressed the cross-coupling reaction of Grignard reagents with enol triflates, acid chlorides and dichloroarenes,³¹⁴ the use of low-valent iron species as catalysts,³¹⁵ as well as the application of these methodologies to the total synthesis of elaborated molecules.³¹⁶

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