Iron-catalyzed C-N bond formations

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This thesis is mainly concerned with the development and application of iron-catalyzed reactions for the synthesis of nitrogen-containing organic compounds. Oximes were synthesized by a novel iron-catalyzed nitrosation of olefins with tert-butyl nitrite and sodium borohydride. Succinimides and maleimides were prepared by employing an iron-catalyzed carbonylation of internal alkynes with ammonia as a key step. This efficient method was applied for the synthesis of natural products and interesting organic building blocks. Furthermore, the thesis describes the development of an efficient protocol for the synthesis of various nitroolefins. Finally, a synthesis of propargyl amines by Shvo-catalyzed alkynylation reaction is presented.

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Abbreviations

Ac Acetyl
acac Acetonylacetate
Ar Aryl group
Bn Benzyl
Boc tert-Butyloxycarbonyl
\( i\)-Bu iso-Butyl
\( t\)-Bu tert-Butyl
cat. Catalyst
CBz Carboxybenzyl
Cp \( \eta^5\)-Cyclopentadienyl
DCE 1,2-dichloroethane
DDQ 2,3-Dichloro-5,6-dicyanobenzoquinone
\((DHQD)\text{2Pyr}\) Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
dmeda \( N,N'\)-Dimethylethane-1,2-diamine
DMF \( N,N'\)-Dimethylformamide
DMSO Dimethyl sulfoxide
\( dr\) Diastereomeric ratio
\( ee\) Enantiomeric excess
emim BTA Ethylmethylimidazolium bis[(trifluoromethyl)sulfonyl]amide
equiv Equivalent
Et Ethyl
h Hour
\( n\)-Hex \( n\)-Hexyl
Me Metyl
min Minute
MS Molecular sieves
MW Microwave
Ns 4-Nitrobenzenesulfonyl
Nu Nucleophile
OTf Triflate (trifluoromethanesulfonate)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Pc</td>
<td>Phthiocyanine</td>
</tr>
<tr>
<td>Pd/C</td>
<td>Palladium on carbon</td>
</tr>
<tr>
<td>PG</td>
<td>Protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>Pip</td>
<td>Piperidine</td>
</tr>
<tr>
<td>i-Pr</td>
<td>iso-Propyl</td>
</tr>
<tr>
<td>n-Pr</td>
<td>n-Propyl</td>
</tr>
<tr>
<td>R</td>
<td>Organic group</td>
</tr>
<tr>
<td>rac</td>
<td>Racemic</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Ses</td>
<td>2-Trimethylsilylethanesulfonyle</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TPP</td>
<td>Tetraphenylporphyrin</td>
</tr>
<tr>
<td>Ts</td>
<td>Toluene-(p)-sulfonyle</td>
</tr>
</tbody>
</table>
1 Introduction

Due to the ubiquitous presence of nitrogen-containing compounds in a broad spectrum of natural and synthetic organic molecules,[1] the formation of carbon-nitrogen bonds remains an important challenge in organic synthesis. In the past decades transition metal-catalyzed C-N bond forming processes have become valuable synthetic tools for obtaining amines both in academia and in industry. However, the drawbacks of many catalysts such as high cost and toxicity are obvious. Thus, the development of efficient and environmentally benign synthetic protocols for the synthesis of nitrogen-containing compounds is still highly desirable.

Among the transition metal catalysts, iron is an ideal transition metal because of its ready availability, low price and environmentally friendly features. In this respect, iron-catalyzed reactions for a variety of transformations have increased considerably in literature[2] and it is expected that this research area will increase dramatically in the future.

The focus of the present introduction will be on iron catalyzed C-N bond formations, which constitute also the main topic of the present thesis.
2 Iron-catalyzed C-N bond formations

2.1 Addition reactions

2.1.1 Aza-Michael additions

The conjugate addition of N-nucleophiles to α,β-unsaturated carbonyl compounds, the so-called aza-Michael addition, is an important C-N bond forming process leading to β-amino carbonyl compounds. In the past few years, a large number of alternative procedures have been reported using Cu(OAc)_2·H_2O, LiClO_4, Cu(OTf)_2, Bi(OTf)_3, Bi(NO)_3, CeCl_3·7H_2O/NaI, InCl_3, Ln(OTf)_3.

In 1989 Laszlo and co-workers reported the success of Michael addition of amines to acrylates by the use of FeCl_3 leading to amino adducts in high yields under mild conditions. Moreover, FeCl_3 has also been proven to be effective for the conjugate addition of secondary amines to the weak acceptor α-acetamidoacrylate. Xia et al. developed a new system for the conjugate addition of chalcones 1 and cyclic enones 6 with unactivated weakly nucleophilic carbamates 2 and 3 using simple FeCl_3·6H_2O as an effective catalyst and Me_3SiCl as an additive in CH_2Cl_2 to give β-amino ketones 4-5, 7-8 (Scheme 1).

![Scheme 1. Aza-Michael reaction of enones with carbamates.](image-url)
More attractive catalytic systems for aza-Michael addition of ethyl acrylate and electrophilic \( \alpha,\beta \)-unsaturated compounds with amines were also reported (Scheme 2).\textsuperscript{[15]} Among several transition-metal-based Lewis acid catalysts, FeCl\(_3\)-6H\(_2\)O was found to be effective for the reaction in aqueous solution. In general, only the mono-addition products 9-12 were achieved; however, the reaction of PrNH\(_2\) with ethyl acrylate gave quantitative yield of the disubstituted product 13.

### 2.1.2 Hydroaminations of non-activated alkenes and alkynes

Hydroamination, the direct addition of N-H bonds to C-C multiple bonds, is an attractive and green method for the synthesis of amines, imines and enamines because the reaction exhibits high atom economy (Scheme 3).\textsuperscript{[16]} The high activation energy barrier of the reaction can be avoided in principle by the use of catalysts to change the reaction path of the nucleophilic substrates. In general, the catalytic hydroamination of non-activated olefins has been a major challenge for modern catalysis research. Various protocols have been developed by using different catalysts such as Brønsted acids, Lewis acids, alkaline metals, lanthanides, actinides, early transition metals (Ti, Zr, Hf, V, Ta), late transition metals (Ru, Rh, Ir, Ni, Pd, Pt, Cu, Ag, Au). Nevertheless, a generally applicable method is still missing.
2 Iron-catalyzed C-N bond formations

![Scheme 3. Hydroamination of alkenes and alkynes.](image)

The first report of intramolecular iron-catalyzed hydroamination of unactivated olefins was published by Takaki and co-workers in 2006. Among the transition-metal catalysts tested, e.g. FeCl₃, FeCl₃·6H₂O, FeCl₂·4H₂O, Fe(NO₃)₃, Fe₂(SO₄)₃, Fe(acac)₃, Cu(OTf)₂, AgOTf, CoCl₂, NiCl₂, CuCl₂ and ZnCl₂, FeCl₃·6H₂O showed the best catalytic performance in this reaction. The product yields were greatly influenced by the solvents employed. It was found that DCE was the best solvent. In most cases, 5-exo-trig cyclization products were formed preferentially compared to the 6-endo-trig cyclization product.

![Scheme 4. Intramolecular hydroamination of aminoolefins.](image)

In 2007, hydroamination of norbornene (17) with amines has been reported by Takaki et al. and Li et al. Here, the cationic catalyst, Fe(OTf)₃ derived from FeCl₃ and AgOTf, was found to produce the active catalyst for the intermolecular hydroamination of 17 and TsNH₂ while the use of FeCl₃ alone for the addition of 2,5-dichloroaniline (19) to 17 needed more severe conditions.
Recently, Prim and Campagne et al. published the intermolecular FeCl₃-catalyzed hydroamination of styrenes (Scheme 6) and the use of a new catalytic combination (FeCl₃:PdCl₂ = 2:1 mol%) in preparation of indoles and bis(indolyl)methanes (Scheme 7).[19] Hydroamination of vinylarenes 21 with deactivated nitrogen nucleophiles could be catalyzed by FeCl₃ without any ligand or co-catalyst. However, some limitations such as steric hindrance at either α- or β-position of styrene and the presence of electron-withdrawing group on the phenyl ring were found in the reaction (Scheme 6).[19a]
Intramolecular hydroamination of alkynylanilines 23 to give indoles have been reported in the presence of low loadings of the bimetallic catalyst system (FeCl₂:PdCl₂ = 2:1 mol%) in open-air flasks. It is believed that O₂ and the iron complex act as reoxidants for the palladium catalyst. Electron-deficient alkynes needed longer reaction time and only lower yield were observed. This methodology was also extended to a one-pot synthesis of bis(indolyl)methanes 26 and the tri-substituted indole 28 (Scheme 7).[19b]

2.1.3 Alkene diaminations

1,2-Diamines represent an important functional motif, which can be found in numerous natural products and pharmaceutical targets as well as various building blocks for asymmetric organic synthesis (Figure 1).[20] In the past catalytic diaminations of alkenes to achieve vicinal diamines have been performed with palladium, nickel, and copper catalysts.[21]
An iron-catalyzed 1,2-diamination reaction of $\alpha,\beta$-unsaturated ketones 37 and esters 39 has been reported by Li et al. in 2002, which led to the formation of imidazoline derivatives 38 and 40, respectively (Scheme 8). The electrophilic diamination of electron-deficient alkenes by using $N,N$-dichloro-$p$-toluenesulfonamide (TsNCl$_2$) as electrophilic nitrogen source, acetonitrile as the nucleophilic nitrogen source and FeCl$_3$-PPh$_3$ as the catalyst occurred easily at room temperature without the need of inert atmosphere. A year later, the same authors discovered that related Ritter-type electrophilic diamination of alkenes proceed without the use of any metal catalyst. However, the reactions needed longer reaction times and lower product yields were achieved in most cases. The proposed mechanism involves the formation of aziridinium intermediate A, which is further attacked at the $\beta$-position by chlorine anion to generate $N$-chloro haloamine intermediate B. Subsequent S$_{N}$2 displacement with MeCN affords a nitrinium intermediate C. These two steps are responsible for the high stereoselectivity.
2.1.4 Aminochlorinations

Bach et al. have shown that 2-alkenyloxycarbonyl azides 41 and 43 cyclize to the corresponding 4-(chloromethyl)oxazolidinones 42 and 44, respectively in the presence of FeCl$_2$ with TMSCl as a source of chloride ions in EtOH (Scheme 9).\[24,25\] Good selectivities for trans-42 have been obtained and aziridine intermediates, which are known to occur from these azide substrates, have not been observed. To study the mechanism, the reactions of azidoformates 43 have been studied by comparing the Fe(II)-catalyzed reaction and the thermal reaction. The latter reaction of 43a and 43b afforded only erythro-44a in 62% yield and erythro-44b and 42% yield, respectively. These evidences suggested that Fe(II)-catalyzed intramolecular aminochlorination occurred via radical intermediate H. The threo-selectivity of 44 in catalytic reaction was found to depend on the degree of the restricted rotation around the C-C single bond of intermediate H.
2.1.5 Aminohydroxylations

1,2-Aminoalcohols are another important class of compounds, which are present in many natural products, bioactive synthetic compound, organocatalysts and chiral auxiliaries (Figure 2). Among the known catalytic aminohydroxylations especially the osmium-catalyzed Sharpless asymmetric aminohydroxylation has proven to be a powerful method for the preparation of vicinal amino alcohols. In addition, palladium and copper catalysts have also been shown to be effective catalysts for this addition reaction.
Very recently, Yoon and co-worker have shown that iron(III) complexes catalyze the aminohydroxylation of alkenes by using oxaziridines 56 as terminal oxidants to give regioselectively oxazolidines 57 (Scheme 11).\(^{[31]}\) Interestingly, the reaction proved tolerant of different substitution patterns on the phenyl ring of styrenes and steric hindrance at both $\alpha$– and $\beta$–positions of styrenes as well as to the presence of polar functional groups. Symmetrical and unsymmetrical dienes have been shown to be effective substrates. However, enyne and aliphatic olefins were less reactive and gave lower yield under somewhat modified reaction conditions. This methodology has been extended to the synthesis of ($\pm$)-octapamine (see chapter 2.4.2).
### 2.2 Cycloadditions

#### 2.2.1 [2+1]-Cycloadditions (Aziridinations)

Aziridines, three-membered nitrogen heterocycles, are important moieties found in many bioactive natural products (Figure 3).\[^{[32]}\] Due to their high chemical and biological activity, aziridines play an important role in organic synthesis and in pharmaceuticals.\[^{[33]}\] Various transition metals have been employed in aziridination including Cu, Rh, Mn, Ru, Ag, Au, Co, and also Fe.\[^{[34]}\] Catalytic aziridination can proceed via two different routes: one involving nitrene transfer to olefins, and the other one involving carbene or its equivalent transfer to imines (Scheme 12).\[^{[33b,c]}\]

![Scheme 11. Aminohydroxylation catalyzed by iron(III) complexes.](image)

![Figure 3. Examples of natural products containing aziridines.](image)
Iron(III) porphyrin and iron(IV) corrole complexes were recognized to be effective catalysts for nitrene transfer reactions.\textsuperscript{[35,36]} The aziridination catalyzed by these complexes with [(tosylimido)iodo]-benzene (PhINTs) as a nitrene source has been reported by Mansuy and co-workers.\textsuperscript{[35b-d]} However, the reaction has suffered from many disadvantages including commercial unavailability, high price and insolubility of the reagent as well as the generation of PhI as byproduct. Therefore, different nitrene sources have been investigated. For example, Zhang \textit{et al.} developed a novel Fe(Por)Cl/bromamine-T catalytic system for aziridination, which works under mild condition with alkene as limiting agent. This catalytic system was suitable for various alkenes such as aromatic, aliphatic, cyclic and acyclic olefins as well as \(\alpha,\beta\)-unsaturated ester leading to the desired aziridine in good yield, although the stereospecificity of 1,2-disubstituted olefins was only moderate to low (Scheme 13).\textsuperscript{[35a]} Iron(II) phthalocyanine, structurally similar to iron porphyrin, also catalyzed aziridination of 4-methylstyrene with PhINTs but it was found to be less active than copper(II) phthalocyanine.\textsuperscript{[37]} These catalytic aziridination are assumed to proceed via an iron-nitrene intermediate I (Scheme 13).
The use of non-heme iron complexes in catalytic aziridination has been studied by Latour et al.\textsuperscript{[38]} and Halfen et al (Figure 4).\textsuperscript{[39]} Latour and Avenier reported that the mixed-valent diiron complex \(68\) catalyzed aziridination in the presence of PhINTs and large amounts of olefins (\(68\):PhINTs:olefin = 0.05:1:2000), giving \(N\)-tosylaziridines in 50-69% yields.\textsuperscript{[38]} The mononuclear non-heme iron(II) complexes \(69\)–\(70\) have been employed as the olefin aziridination catalysts by Halfen and co-workers.\textsuperscript{[39]} The reaction systems yielded aziridines in moderate to high yields and required only small excess of olefins (\(69a\) or \(70\):PhINTs:olefin = 0.05:1:5-25). With respect to the mechanism, Hafen and Phillips et al. demonstrated experimental and computational studies of aziridination of \(cis\)-1-phenylpropene. From these results, it was suggested that the reaction proceed along two pathways after a common intermediate \(J\).\textsuperscript{[39a]}

Bolm and co-workers described iron(II) triflate-catalyzed aziridination reactions in the presence of preformed iminiodinanes PhINSO\(_2\)Ar with excess of olefins affording moderate to good yields of \(71\). Asymmetric aziridination have also been performed with this catalytic system in the presence of tridentate ligand \(L1\) (Scheme 14).\textsuperscript{[40]} Later, the same authors developed the more practical and efficient system containing Fe(OTf)\(_2\), quinaldic acid \(L2\) and an ionic liquid for the conversion of olefins into aziridines \(72\) by using only one equivalent olefins (Scheme 15).\textsuperscript{[41]}
Scheme 14. Aziridination catalyzed by iron(II) triflate.

Scheme 15. Aziridination catalyzed by iron(II) triflate and promoted by ionic liquid.

Iron-based Lewis acid catalysts, [(η⁵-C₅H₅)(CO)₂Fe(THF)]⁺[BF₄]⁻ (76) and [(η⁵:η¹-C₅H₄CH(Ph)OPPh₂)Fe(CO)(THF)]⁺[BF₄]⁻ (77), and iron-pybox complexes (78) were employed in the reaction between imine 73 and ethyl diazoacetate (74) by Hossain et al. (Scheme 16).[42] In these reactions, predominantly cis-aziridine 75 was formed. Furthermore, the iron Lewis acid 76 has also proven to be an efficient catalyst for the reaction between PhINTs and excess olefins (2-5 equiv) to afford aziridines up to 85%.[43]

Scheme 16. Aziridination catalyzed by iron Lewis acid catalysts and iron-pybox complexes.
2.2.2 [2+2]-Cycloadditions

Formal [2+2]-cycloaddition reaction of iron(II) vinylidene complexes was reported by Barrett and co-workers. Reaction of cationic iron(II) vinylidenes 79 with imines 80 and thiazolines 83 provided the corresponding azetidinylidene complexes 81 and 84. Subsequent oxidation of these complexes led to mono- or bicyclic \( \gamma \)-lactams 82 and 85 (Scheme 17).

\[ \begin{align*}
\text{Scheme 17. Iron(II) vinylidenes in \( \gamma \)-lactam synthesis.}
\end{align*} \]

2.2.3 [2+3]-Cycloadditions

The [2+3]-cycloaddition of nitriles 86 and trimethylsilyl azide (87) proceed in the presence of a catalytic amount of Fe(OAc)\(_2\) in a 9:1 mixture of DMF and MeOH at 80 °C (Scheme 18). It should be noted that the purity of the iron source affected the yield of the tetrazole products. Generally, when 99.995% (Aldrich) Fe(OAc)\(_2\) was employed lower yields of 88 were obtained than when the reactions were run using 95% (acros) Fe(OAc)\(_2\), making it likely that other metals are involved in this catalysis.

\[ \begin{align*}
\text{Scheme 18. Formal [2+3] cycloaddition to 5-substituted 1H-tetrazoles 88.}
\end{align*} \]
2.2.4 [4+1]-Cycloadditions

The construction of pyrrolinones 90 via [4+1]-Cycloaddition of allenyl imines 89 and CO employing Fe(CO)₅ as a catalyst have been described by Eaton et al. (Scheme 19). The iron-catalyzed photochemical reaction proceeded under mild condition (22 °C, 80 mM CO) with fluorescent light providing good yields of 90. High stereoselectivity is achieved when the terminal allene groups are tert-butyl and methyl.

\[
\begin{align*}
\text{Scheme 19. Formal [4+1] cycloaddition to 3-alkylidene-4-pyrrolin-2-ones 90.}
\end{align*}
\]

2.2.5 [2+2+1]-Cycloadditions

Catalytic intermolecular hetero-Pauson-Khand-type reactions, a formal [2+2+1] cycloaddition reaction, between 1,4-diazabutadienes, carbon monoxide and ethylene to give pyrrolidin-2-one 92 has been demonstrated by Imhof and Anders et al. (Scheme 20). The reaction proceeded with complete regioselectivity meaning that only the active imine was activated during the catalysis. The imine moiety next to the oxazine oxygen was more reactive than the other one.

\[
\begin{align*}
\text{Scheme 20. Formal [2+2+1] cycloaddition to spirolactams 92.}
\end{align*}
\]
2.2.6 [2+1+1+1]-Cycloadditions

In 2000, Periasamy et al. observed that the addition of excess primary amines to iron complexes, formed in the reaction of alkynes with a mixture of Fe(CO)_5/NaBH_4/CH_3COOH, provided the corresponding succinimides 93 in moderate to good yields after CuCl_2·2H_2O oxidation (Scheme 21).[48] However, this reaction had the drawback of using stoichiometric amount of the Fe(CO)_5 and requiring several steps to obtain the respective succinimides.

\[
\text{Fe(CO)}_5 + \text{NaBH}_4 \quad \rightarrow \quad \text{succinimide 93}
\]

Scheme 21. The synthesis of succinimides 93 using iron carbonyl complexes.

Recently, we discovered that the formation of succinimides 95 via [2+1+1+1]-annulation of alkynes, CO and ammonia also proceeds in the presence of catalytic amounts of Fe_3(CO)_12 (Scheme 22).[49] The oxidative dehydrogenation of succinimides 95 by DDQ or MnO_2 afforded maleimides 96. Notably, a straightforward synthesis of maleimide 98 from alkyne 97 was achieved with only one final purification step in high yield (Scheme 23). This method has been successfully used as a key step in the total synthesis of several bioactive natural products (see chapter 2.4.3).

\[
\text{alkyne 97} \quad \rightarrow \quad \text{maleimide 98}
\]

Scheme 22. Formal [2+1+1+1] cycloaddition to succinimides 95.
Very recently, Jana and co-workers reported a novel and convenient one-pot procedure for the synthesis of highly substituted pyrroles 103 by using amines 99, aldehydes 100, 1,3-dicarbonyl compounds 101, and nitroalkanes 102 (Scheme 24). This four-component coupling reaction is believed to proceed via the in situ-generated β-enamino carbonyl compounds K and nitroalkene L followed by Michael reaction and cyclization to afford the corresponding pyrroles in moderate to high yields. Notably, the reaction could be carried out smoothly without exclusion of moisture or air from the reaction mixture.

2.2.7 1,3-Dipolar cycloadditions

Itoh and co-workers have demonstrated a convenient and efficient procedure for the one-pot synthesis of 3-benzoyl- and 3-acetyl-1,2,4-oxadiazole derivatives 106 (Scheme 25). The mechanism of this reaction involved enolization to yield intermediate O followed by nitration to generate α-nitro ketone P. Acid-catalyzed dehydration of P provided nitrile oxide Q, which
underwent 1,3-dipolar cycloaddition with nitrile 105 to give the 1,2,4-oxidiazole 106 in low to excellent yields depending on the stability of the nitrile oxides and the reactivity of nitriles in 1,3-dipolar cycloaddition.

\[
\begin{align*}
\text{O} &\quad + \quad \text{R}^1\text{C} \equiv \text{N} \quad \xrightarrow{\text{Fe(ONO}_2\text{)}_3} \quad \text{O} \quad \text{R}^1\text{C} \equiv \text{N} \\
\text{104a} \quad \text{R} = \text{Me} &\quad \text{105} \\
\text{104b} \quad \text{R} = \text{Ph} &\quad \text{Fe(ONO}_2\text{)}_3 \\
\text{p} &\quad \text{OH} \quad \xrightarrow{\text{CH}_3\text{CN, reflux} \quad 3-34 \text{ h}} \quad \text{R}^1\text{C} \equiv \text{N} \quad \text{R}^1 \\
\text{P} &\quad \xrightarrow{\text{61-100\%}} \quad \text{OH} \quad \text{R}^1\text{C} \equiv \text{N} \\
\text{Q} &\quad \xrightarrow{\text{R}^1\text{C} \equiv \text{N}} \quad \text{OH} \quad \text{R}^1\text{C} \equiv \text{N} \\
\end{align*}
\]

Scheme 25. One-pot synthesis of 1,2,4-oxidiazoles 106.

2.3 Substitution reactions

2.3.1 Nucleophilic substitution of non-activated C-X bonds

The substitution reaction of azides 107 by \(N,N\)-dimethylhydrazine in the presence of catalytic amounts of \(\text{FeCl}_3\cdot6\text{H}_2\text{O}\) led to \(N,N\)-dimethylhydrazone 108 in high to excellent yields (Scheme 26).\(^{[52]}\) The reaction was postulated to proceed \(\text{via}\) tautomerization of azide 107a to the more reactive intermediate S followed by hydrazine attack and proton transfer to give intermediate U. The subsequent expulsion of nitrogen and ammonia provided hydrazone 108a.

\[
\begin{align*}
\text{R} &\quad \text{N}_3 \quad \xrightarrow{\text{FeCl}_3 \cdot 6\text{H}_2\text{O} \quad (10 \text{ mol\%})} \quad \text{H}_2\text{N} \quad \text{NMe}_2 \\
\text{107} &\quad \text{R}^1 \quad \text{N}_3 \quad \xrightarrow{\text{CH}_3\text{CN, reflux} \quad 3-34 \text{ h}} \quad \text{81-100\%} \\
\text{108} &\quad \text{R}^1 \quad \text{N}_3 \quad \xrightarrow{\text{H}_2\text{N} \quad \text{NMe}_2} \quad \text{R}^1 \quad \text{N}_3 \quad \text{NMe}_2 \\
\text{R} &\quad \text{alkyl, Ar, Bn} \\
\text{R}^1 &\quad \text{H, CH}_3 \\
\end{align*}
\]

Scheme 26. The substitution reaction of azides 107 by \(N,N\)-dimethylhydrazine.
The reaction of nitriles with benzylic alcohols or tert-butyl acetate to generate amides, the so-called Ritter reaction, is well known to be catalyzed by Bronsted acids, Nafion and bismuth triflate. Recently, the groups of Reymond and Cossy reported that Ritter reactions are also catalyzed by FeCl₃·6H₂O (10 mol%) (Scheme 27). In general, the reactions of benzylic alcohols 109 with nitriles 110 were performed without solvent (conditions A). Except for the reaction with acrylonitrile (110b), cumene was used as the solvent (conditions B). The reaction of 109d with MeCN (110a) was conducted at lower temperature (50 °C) to obtain the corresponding amide. In contrast, the reaction of 109a with 110a at 70 °C provided ether 112, which could be transformed to 111a in the presence of FeCl₃·6H₂O at 150 °C. The ether formation from benzylic alcohol proceeded in the presence of FeCl₃ or Fe(NO₃)₃. Therefore, it was believed that the reaction involved intermediates V-X which can be attacked by nitrile. The synthesis of tert-butyl amides 113 was also achieved from the reaction of nitriles 110c-f with tert-butyl acetate in moderate to high yields under conditions B.

\[
\begin{align*}
\text{Ar} & \text{R} & \text{FeCl}_3\cdot6\text{H}_2\text{O} (10 \text{ mol%}) & \text{Ar} & \text{R}^1 \\
109 & & 110a-c, \text{H}_2\text{O (2 equiv)} & 150 ^\circ\text{C}, 0.5-15 \text{ h} & 41-96% \\
\text{condition A} = \text{alcohol (1 mmol), nitrile (1 mL), sealed tube.} & \text{condition B} = \text{alcohol (1 mmol), nitrile (3 mmol), cumene (1 mL), sealed tube.}
\end{align*}
\]

Scheme 27. Iron-catalyzed Ritter reaction.

### 2.3.2 Allylic and propargylic aminations

 Allylamines are basic building blocks in organic chemistry and serve as useful substrates for the synthesis of a wide range of compounds of biological interest such as alkaloids, α- and β-amino acids, etc. Several transition metal-catalyzed allylic amination reaction using Pd, Ir,
Ru and Rh as metal sources have been investigated.\textsuperscript{[62]} Iron catalysis of this reaction has also been developed. In 1994, Jørgensen et al.\textsuperscript{[63]} and Nicholas et al.\textsuperscript{[64]} published the preparation of allylamines from alkenes and phenylhydroxylamine by using iron phthalocyanine [Fe(Pc); condition A] and/or iron salts (condition B) as the catalysts (Scheme 28).

![Scheme 28. Allylic amination of phenylhydroxylamine with alkenes.](image)

Under conditions A, only aromatic alkenes were efficiently converted into the corresponding allylamines (115a, 115d, 115e). In contrast, aliphatic internal alkenes gave significantly better yields of products (115f, 115g) under the conditions B. The allylic amination reactions were found to proceed via different mechanisms depending on the catalytic systems chosen. From mechanistic studies of this reaction catalyzed by Fe(Pc),\textsuperscript{[65]} it was proposed that the reaction occurs through ene reaction of the alkene and the reactive nitrosobenzene (PhNO), giving the allylic hydroxylamine 116, which was reduced to allylamine 115h. The role of this iron complex involved both the oxidation of phenylhydroxylamine to PhNO and the reduction of the hydroxylamine to allylamine. In case of an Fe(II)/Fe(III) catalytic system, it was found that the nitrosobenzene complex Y was formed, which appeared to be the active aminating agent in the reaction.\textsuperscript{[66]}
Nicholas and co-workers have extended these studies by using more readily available amination agents, e.g. nitroarenes, instead of phenylhydroxylamine (Scheme 29). The reaction of nitroarenes and alkenes took place in the presence of carbon monoxide using \([\text{CpFe(CO)}_2]\)_2 as catalyst. 1,1-Disubstituted alkenes have shown to be good substrates, providing allylamines 115a, 115i in high yields. The electronic effects of substituents on aromatic ring of nitroarenes had a significant impact on the reaction outcome. Electron-poor nitroarenes gave much better results than electron-rich nitroarenes. In the presence of near UV light (>300 nm), the reaction performed under milder conditions.

Plietker developed a catalytic system for allylic amination reactions of allyl carbonates 118 with primary anilines, which were catalyzed by \([\text{Bu}_4\text{N}]\text{[Fe(CO)}_3\text{(NO)}]\) (Scheme 30). The reaction afforded the desired allylamines 119 in high regioselectivity, in which the new C-N bond was formed selectively at the carbon bearing the carbonate group. When chiral enantiopure allyl carbonates 121 were employed, (S)-122 were obtained in high stereoselective retention of configuration through a \(\sigma\)-allyl metal intermediate in the proposed mechanism.
In 2008, Jana et al. published a mild and environmentally friendly allylic amination reaction of allylic alcohols 123 in the presence of catalytic amount of FeCl₃ (Scheme 31). The reaction of allylic alcohols 123 and their isomers 124 with carboxamides or p-toluenesulfonamide led to the single products 125 regioselectively. This fact proved that the reaction involved the same, delocalized allylic cation intermediate via SN1 mechanism.

Recently, Reymond and Cossy and their co-workers have reported intramolecular allylic amination reactions of 126 to generate cis-2,6-piperidines 127 (Scheme 32). It was suggested from the results that the amino-protecting group affected the reaction outcome more than the R substituent. N-Tosyl derivatives showed the best activity and were transformed to the corresponding cis-2,6-piperidines 127 within short reaction time (30 min) in good to excellent yields (up to 99%) and high diastereoselectivities (cis:trans from 90:10 to >99:1). When N-Boc and N-nosyl protecting groups were used, longer reaction times and/or higher catalyst loadings were necessary to reach high diastereoselectivity. The high diastereoselectivity of 2,6-disubstituted piperidines 127 was achieved by FeCl₃·6H₂O-catalyzed epimerization to the thermodynamically more stable cis-isomer via zwitterionic intermediate Z.
Propargylamines and their derivatives are also important synthetic intermediates in organic synthesis\(^{[73]}\) and for biologically active compounds.\(^{[74]}\) Several known methods to prepare propargylamines are based on propargylic substitution reactions\(^{[75]}\) of propargylic alcohol derivatives with nitrogen nucleophiles. The Nicholas reaction with nitrogen nucleophiles, which requires a stoichiometric amount of \([\text{Co}_2(\text{CO})_8]\) is known to be effective for propargylic amination.\(^{[76]}\) To overcome the disadvantages of the Nicholas reaction, several transition-metal catalyzed propargylic aminations have been developed.\(^{[77]}\) With respect to iron, the only catalytic substitution reaction of propargylic alcohols with \(N\)-nucleophiles has been reported by Zhan \(\textit{et al.}\) in 2006 (Scheme 33, 34).\(^{[78]}\) The reactions of \(128\) bearing internal or terminal alkyne moieties with amides in the presence of a catalytic amount of \(\text{FeCl}_3\) (5 mol\%) proceeded smoothly in acetonitrile at room temperature to give the corresponding propargylic amides \(129\) in moderate to high yields (Scheme 33). Acetamide, aniline, and piperidine were also attempted as the \(N\)-nucleophiles but no propargylic substitution reaction took place under this condition. It should be noted that \(C\)-, \(O\)- and \(S\)-nucleophiles can also be used in this method.

Scheme 32. Intramolecular allylic amination of amino allylic alcohols 126.

\[
\begin{align*}
\text{FeCl}_3 \cdot 6\text{H}_2\text{O} (5\text{-}10 \text{ mol}\%) \\
\text{C}_2\text{H}_5\text{OH}, \text{rt}, \text{3.5-}10 \text{ h} \\
\text{dr} = 90\text{%-}100\%
\end{align*}
\]

Scheme 33. Propargylic substitution reaction of propargylic alcohols 128 with nitrogen nucleophiles.
This methodology has been extended further for the synthesis of substituted thiazoles 131 directly from propargylic alcohols 128, amides 130 and Lawesson’s reagent in a one-pot procedure (Scheme 34).[79] The synthesis process involved the iron-catalyzed substitution reaction of propargylic alcohol 128 with amide 130 to generate propargylic amide 129 followed by sulfuration with Lawesson’s reagent giving thioamide B’. Subsequent cycloisomerization of thioamides B’ leads to the desired product 131 with complete regioselectivity.

We have recently reported the synthesis of propargylamines by an alternative method: the reaction of non-activated aliphatic amines with silylated alkynes by employing the so-called Shov catalyst.[80] The reaction was postulated to proceed via the alkynylation of the in situ generated iminium ion with the terminal alkyne.

2.3.3 N-Arylations

N-Aryl-amines, -amides, -pyrazoles, and -imidazoles are known to exhibit numerous interesting biological activities (Figure 5).[81] Thus, transition metal-catalyzed N-arylations,[82] have become important methods for the synthesis of this type of compounds. In general, C-N cross-coupling reactions have been demonstrated with palladium[83] and copper[84] catalysts. However, also iron catalysts have attracted significant attention for coupling reactions lately.
In 2007, Taillefer and co-workers reported a novel iron/copper catalytic system for N-arylation of aryl halides 137 with various nitrogen heterocycles (pyrazole, imidazole, pyrrole, triazole, indole) or cyclic amide derivative (Scheme 35). Coupling reactions of aryl iodides and few aryl bromides were performed under mild conditions (90 °C) in the presence of Fe(acac)₃ (30 mol%) and CuO (10 mol%) as pre-catalysts and cesium carbonate as base. In case of the electron-rich aryl bromides, iodoaniline and activated aryl chlorides higher temperatures (120 °C or 140 °C) were necessary. As an advantage of this catalytic system no side-product was formed during the catalysis.

Another iron/copper catalytic system for the cross-coupling reaction of N-heterocycles with aryltrimethoxysilanes or vinyltrimethoxysilane was developed by Li et al. Here, N-arylations of imidazoles and triazoles were carried out by using FeCl₃/Cu and TBAF as base under air atmosphere in the absence of solvents to afford the corresponding products in moderate to excellent yields.

Shortly thereafter, Bolm et al. published the first genuine iron-catalyzed N-arylation. The active catalytic system consisted of FeCl₃ (10-20 mol%), dmdea (20-40 mol%) as chelating ligand and base (K₂CO₃, K₃PO₄ or Cs₂CO₃) without the need of added copper. Temperature and solvent selection had a significant influence on the catalyst performance. The best result was
obtained when the reaction was carried out in toluene at 135 °C. The reaction condition has been applied successfully to the cross-coupling reaction of aryl iodides with various nitrogen nucleophiles (Scheme 36-37).\[^{[87-90]}\] Pyrazole has been tested to couple with several aryl iodides and bromides.\[^{[87]}\] However, aryl iodides were more reactive than aryl bromides and led to the desired product in higher yields. A limitation for this method was that ortho-substituted aryl iodides gave only poor yields of the coupling products. Electron-rich and -poor aryl iodides reacted with a range of N-heterocycles (indole, azaindole, and pyrrolidin-2-one),\[^{[87]}\] benzamides and aliphatic amides\[^{[87,88]}\] as well as sulfoximines\[^{[89]}\] leading to the corresponding products (138, 141 and 142) in moderate to excellent yields. Aromatic and alkyl amines failed to react under these reaction conditions (Scheme 36).

\[
\text{Scheme 36. } N\text{-Arylation of aryl iodides 137 with sulfoximine 139 or amides 140.}
\]

Acetanilides were also suitable substrates under slightly modified condition (using Cs\textsubscript{2}CO\textsubscript{3} as the base instead of K\textsubscript{2}CO\textsubscript{3} or K\textsubscript{3}PO\textsubscript{4}) (Scheme 37).\[^{[90]}\] This protocol allowed the preparation of a range of diarylamines 144 in a one-pot procedure by iron-catalyzed N-arylation of aryl iodides 137 with acetanilides 143 followed by cleavage of the acetyl group. Steric effects of ortho substituents of both aryl iodides 137 and acetanilides 143 play an important role on the cross-coupling reactions. When ortho-substituted aryl iodides were employed, only trace amount of the coupling product could be observed. The ortho substituents in acetanilides were better tolerated and afforded moderate yields of the desired products.
Scheme 37. N-Arylation of aryl iodides 137 with acetanilides 143.

Recently, Buchwald and Bolm reported that the purity of the metal salt and its commercial source had a large effect on the catalyst performance (Table 1).\textsuperscript{[91]} N-Arylation reaction of pyrazole with 4-iodoanisole with >99.99% FeCl\textsubscript{3} gave lower yield than that with >98% FeCl\textsubscript{3}. The better yield is observed when 5-10 ppm Cu\textsubscript{2}O was used together with >99.99% FeCl\textsubscript{3}. The authors suggested that trace amount of other metals, especially copper, are responsible for the catalytic activity.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
FeCl\textsubscript{3} & Cu\textsubscript{2}O & Yield [%] (GC) \\
\hline
>98% (Merck) & - & 87  \\
>98% (Aldrich) & - & 26  \\
>99.99% (Aldrich) & - & 9  \\
>99.99% (Aldrich) & 5 ppm Cu\textsubscript{2}O & 78  \\
>99.99% (Aldrich) & 10 ppm Cu\textsubscript{2}O & 79  \\
- & 5 ppm Cu\textsubscript{2}O & 77  \\
- & 5 ppm Cu\textsubscript{2}O & 23\textsuperscript{a}  \\
\hline
\end{tabular}
\caption{N-Arylation reaction of pyrazole catalyzed by different FeCl\textsubscript{3}/Cu\textsubscript{2}O.}
\end{table}

Liu and co-workers have developed a novel iron catalyst system for C-N cross-coupling reactions based on the use of Fe\textsubscript{2}O\textsubscript{3} (10 mol\%), L-proline (20 mol\%), and NaO\textsubscript{t}Bu (2 equiv) in DMSO at 135 °C for 24 h.\textsuperscript{[92]} A variety of nitrogen-containing compounds such as aliphatic primary amines, aliphatic secondary amines, benzylamine, aniline, and \textit{N}-heterocycles (pyrazole, indole and benzoimidazole) were coupled with iodobenzene but only aliphatic primary amines...
and aliphatic secondary amines afforded the desired products in good yields (70-90%). A range of substituted aryl halides were also tested with morpholine under the optimized reaction condition. Commonly, electron-rich and -poor substituted aryl halides behave similarly. However, the impact of steric hindrance was crucial. *Ortho*-substituted aryl halides gave much lower yields than *meta*- and *para*-substituted aryl halides. In many cases of *para* - and *ortho*-substituted aryl halides, a mixture *cine* - and *ipso*-substitution\(^9\) products was obtained via benzyne intermediates.

An iron-catalyzed process using water as environmentally friendly reaction media under operationally convenient conditions has been reported by Teo.\(^{94}\) The best system explored involved the combination of FeCl\(_3\) (10 mol%), dmeda (20 mol%), and K\(_3\)PO\(_4\)·H\(_2\)O (2 equiv). At 125 °C within 36 h, N-arylation reaction of pyrazole with sterically unhindered aryl iodides gave the desired products in high yields (70-88%). In case of aryl bromides and sterically hindered aryl iodides, the coupling products were obtained in moderate to low yields (17-45%). The method worked also well with the range of nitrogen nucleophiles including indole, 7-azaindole, and benzamide. A similar reaction condition was reported by Kwong *et al.*\(^{95}\) They used FeCl\(_3\)·6H\(_2\)O/rac-*trans*-N,N′-dimethylecyclohexane-1,2-diamine as the catalytic system.
Fu and co-workers have shown keen interest in the synthesis of \(N\)-heterocycles such as benzimidazoles,\(^{[96]}\) quinazolinones,\(^{[97-99]}\) quinazolines,\(^{[98]}\) and 1,2,4-benzothiadiazine-1,1-dioxides,\(^{[99]}\) due to their biological and medicinal activities. Most of the syntheses were accomplished by copper-catalyzed cascade reactions. The only iron-catalyzed example was reported for the cascade synthesis of 1,2,4-benzothiadiazine-1,1-dioxide and quinazolinone derivatives 149 and 151 (Scheme 38).\(^{[99]}\) The reactions of substituted 2-halosulfonamides 147 and substituted 2-bromobenzoic acids 150 with amidine hydrochlorides 148 were carried out in the presence of FeCl\(_3\) (10 mol\%) as the catalyst and CsCO\(_3\) as the base in DMF at 120 °C for 12 h. In both cases, the reaction proceeded via \(N\)-arylation and ring closure to provide 1,2,4-benzothiadiazine-1,1-dioxides 149 and quinazolinones 151 in satisfactory yields.

Recently, Liu \emph{et al}. have published another attractive and environmentally benign catalytic system for iron/copper-catalyzed C-N cross coupling reactions of aryl halides with amines in the presence of water under microwave irradiation.\(^{[100]}\) Optimum results were obtained by applying Fe\(_2\)O\(_3\) (20 mol\%), Cu(acac)\(_2\) (10 mol\%), Cs\(_2\)CO\(_3\) in a mixture of DMSO and H\(_2\)O (1:1) at 150 °C for 30 min without the need of ligand and inert atmosphere. Aliphatic primary and secondary amines, benzylamine, and phenethylamine were effective substrates in the reaction with iodobenzene giving the corresponding products in 66-93% yields. Electronic and steric effects of aryl iodides have an influence on the coupling reaction with morpholine. Iodobenzene as well as
electron-rich and unhindered aryl iodides have been shown to be excellent substrates. The method was extended to the synthesis of indoline, quinazolinone 151a, and N-alkylantranilic acid 153 (Scheme 39).

2.4 The use of iron-catalyzed reactions in natural product synthesis

2.4.1 Iron-mediated synthesis of alkaloids

Tricarbonyliron($\eta^5$-cyclohexadienylium)iron tetrafluoroborates 156, which are useful electrophiles for electrophilic aromatic substitutions of arylamines, are readily synthesized in gram scales.[101] In the presence of catalytic amounts of 1-azabutadiene complexation of cyclohexa-1,3-diene 154 with ironpentacarbonyl afforded tricarbonyliron($\eta^4$-cyclohexa-1,3-diene)iron 155, which is transformed to complex 156a by hydride abstraction using triphenylcarbenium tetrafluoroborate (Scheme 40).[102] The iron complex 156b was prepared in 3 steps from 1,3-dimethoxybenzene as described by Birch.[103]

Knölker et al. used iron-diene complexes 156 in the synthesis of a broad range of biologically active alkaloids such as carbazoles and lycorine alkaloids (Figures 6).[104] The two key steps of the construction of the carbazole skeleton involved first, the C-C bond formation by electrophilic aromatic substitution of arylamines by complexes 156 to generate the arylamine-substituted tricarbonyl($\eta^4$-cyclohexa-diene)iron complex 158 and second, the C-N bond formation and aromatization by oxidative cyclization. Three different processes for oxidative cyclization have been developed and utilized depending on the substitution pattern of arylamines: 1) arylamine cyclization, 2) quinone imine cyclization and 3) oxidative cyclization by air (Scheme 41).[104d]

The iron-mediated arylamine cyclization with concomitant aromatization and demetalation of iron complex 158 to access carbazole derivative 159 in a one-pot procedure was commonly accomplished through oxidation with active manganese dioxide, iodine in pyridine or ferricenium
hexafluorophosphate in the presence of sodium carbonate. From deuterium labelling experiments it is known,\textsuperscript{[105]} that the cyclization is initiated by single electron transfer to give a radical cation D’ followed by \textit{syn}-stereospecific hydrogen transfer to intermediate E’ and subsequent dehydrogenation \textit{via} complexes F’ and G’ to afford 160. Dehydrogenation and spontaneous demetalation of dihydrocarbazole 160 provided the carbazole derivative 159 \textit{via} intermediate H’ (Scheme 41). This method was applied to the synthesis of a variety of carbazoles such as mukoeic acid (167), 4-deoxycarbazomycin B (171), hyellazole (173), antiostatin A and B (176-183), carbazomycin B-C (189-190), and carbazomycin G-H (195-196) (Figure 6).

Iron-mediated quinone imine cyclization of complex 158a to give 4b,8a-dihydrocarbazol-3-one 162 was accomplished through two pathways depending on the oxidant: 1) a two-step oxidation \textit{via} 161 by two differently activated manganese dioxides and 2) a one-pot process by oxidation with thallium trifluoroacetate in buffered ethanol. Demetalation of the tricarbonyliron-complex 162 was achieved by using trimethylamine N-oxide. A selective O-methylation of 3-hydroxycarbazole 163a led to 3-methoxycarbazole 163b (Scheme 41). This strategy was demonstrated for the preparation of several 3-oxygenated carbazoles (Figure 6).

An iron-mediated oxidative cyclization by air was developed as a one-pot procedure for the transformation of the iron complexes 156 and arylamines 157 to give dihydrocarbazole derivatives 160. The reaction involved the cyclization of the \textit{in situ}-generated tricarbonyliron complex 158 with oxygen. Subsequent aromatization and demetalation of the dihydrocarbazoles 160 provided the carbazole derivatives 159 (Scheme 41). This method gives simple access to the synthesis of mukonidine (170), carbazoquinocin C (197), etc. (Figure 6).
Proposed mechanism of iron-mediated arylamine cyclization

Scheme 41. Three different procedures for iron-mediated synthesis of carbazoles.
Oxygenated Tricyclic Carbazole Alkaloids

Murrayafoline A (164)  R = Me  Koenoline (165)  R = CH₂OH
Murrayanine (166)  R = CHO  Mukoeic acid (167)  R = COOH
Mukonine (168)  R = COOMe  2-Methoxy-3-methyl-carbazole (169)  R = Me

4-Deoxycarbazomyzin B (171)  R¹, R² = Me; R³ = H  Carbazostatin (172)  R = (CH₂)₆Me; R¹ = Me; R², R³ = H
Hyellazole (173)  R² = H; R¹ = Me; R³ = H  Isophyllazole (174)  R³ = Me; R¹ = Ph; R² = Me; R³ = H
6-Chlorohyellazole (175)  R¹ = Cl  Antiostatin A₁ (176)  R = (CH₂)₆Me
Antiostatin A₂ (177)  R = (CH₂)₄CH(Me)CH₂Me  Antiostatin A₃ (178)  R = (CH₂)₄CH(Me)₂
Antiostatin A₄ (179)  R = (CH₂)₄CH₂  7-Metoxy-OMethylmukonal (184)  R, R² = Me; R¹ = H
Clausine H (185)  R, R² = Me; R¹ = OMe  Clausine O (186)  R, R¹, R² = H
Clausine K (187)  R = Me; R¹ = OH; R² = Me  Clausine K (187)  R = Me; R¹ = OH; R² = Me

Carbazolequinone Alkaloids

Murrayaquinoine A (194)  R = Me  Carbazomycin A (188)  R, R¹ = Me; R² = H
Carbazomycin G (195)  R = H  Carbazomycin B (189)  R = Me; R¹, R² = H
Carbazomycin C (190)  R = Me, R¹ = H; R² = OMe  Carbazomycin D (191)  R, R¹ = Me; R² = OMe
Carbazomycin E (192)  R = CHO; R¹, R² = H  Carbazomycin A (188)  R, R¹ = Me; R² = H

Furocarbazole Alkaloid

Furostifoline (200)  R = Me; R¹ = H  Furoclausine A (201)  R = CHO; R¹ = OH

Other Alkaloids

Anhydrolycorinone (203)  Hippadine (204)  Demethoxy carbonyldihydro-gambirtannine (205)

Figure 6. Alkaloids prepared by iron-mediated synthetic approach.
2.4.2 Iron-catalyzed synthesis of octapamine

With the success of iron-catalyzed aminohydroxylations (see chapter 2.1.5), Yoon and co-worker have demonstrated the usefulness of their method in the preparation of (±)-octapamine (210) (Scheme 42). The reaction of 4-acetoxystyrene (208) with oxaziridine 56 in the presence of Fe(acac)_3 (5 mol%) provided the regioisomeric 2,5-substituted oxazolidine 209. Finally, acid-mediated oxazolidine cleavage of 209 was carried out with HClO_4 and N-nosyl group was removed by using PhSH/K_2CO_3 to yield (±)-octapamine (210).

![Scheme 42. Synthesis of (±)-octapamine (210).](image)

2.4.3 Iron-catalyzed synthesis of maleimides

Encouraged by the successful synthesis of various maleimides using iron-catalyzed carbonylation as a key step (see chapter 2.2.6), we have applied our catalytic methodology in the synthesis of arcyriarubin derivative 214 (Scheme 43), and himanimide A and B (219 and 220) (Scheme 44).

![Scheme 43. Short synthesis of the arcyriarubin intermediate 214.](image)
For the synthesis of the indolocarbazole 214, the required internal alkyne 213 was prepared by two consecutive Sonogashira cross-coupling reactions. The carbonylation of 213 with ammonia followed by dehydrogenation afforded the Arcyriarubin derivative 214 (Scheme 43).

The preparation of himanimides A and B (219 and 220) was also successfully carried out in 4 and 5 process steps from commercial available materials in 48 and 43 % overall yield (Scheme 44). The internal alkyne 217 was synthesized via alkylation and Sonogashira reaction and transformed to himanimide A (219) by iron-catalyzed aminocarbonylation and subsequent dehydrogenation. The Sharpless catalytic asymmetric dihydroxylation of 219 provided himanimide B (220). The (R)-absolute configuration of C6’ was predicted by the mnemonic device model reported by Sharpless.[107]

Scheme 44. Short synthesis of the himanimide A and B (219 and 220).

2.5 Miscellaneous

2.5.1 Oximations

Based on the use of nitric oxide (NO) in direct nitration reactions to produce nitroolefins,[108] we were interested in the catalytic reaction of olefins with NO or NO equivalents such as tert-
butyl nitrite. It was found that the reaction of aryl-substituted olefins 221 with tert-butyl nitrite and sodium borohydride in the presence of iron(II) phthalocyanine leads to the formation of oximes 222 in moderate to high yields (Scheme 45). The reaction can be performed in a Schlenk tube but when the reaction was performed in autoclave with additional 10 bar H₂, the yield of the desired oxime increased significantly. The reaction was proposed to proceed via σ-alkyliron(III) complex 1’. The reaction of several α,β-unsaturated esters has been investigated under these conditions. Unfortunately, only the hydrogenated product was detected.

**Scheme 45.** Iron-catalyzed synthesis of oximes 222.

### 2.5.2 Paal-Knorr pyrrole synthesis

A simple and practical procedure for preparation of \(N\)-aryl-, \(N\)-alkyl-, \(N\)-sulfonyl-, and \(N\)-acylpyrroles by reaction of functionally diverse amines, arylamides or arylsulfonamides 224 with 2,5-dimethoxytetrahydrofuran (223) has been developed by Azizi et al. (Scheme 46). The reaction is catalyzed by FeCl₃·7H₂O (2 mol%) in water to obtain the heterocyclic products 225 in high to excellent yields.

**Scheme 46.** Iron-catalyzed synthesis of \(N\)-substituted pyrroles 225.

### 2.5.3 Rearrangements

Zhang and co-worker discovered that FeCl₃·6H₂O promotes skeleton rearrangements of 1-aryl-2,3,4,5-tetrahydro-1\(H\)-3-benzazepines to generate tetrahydroisoquinolines in nitrobenzene (Scheme 47). The \(N\)-substituents have great influence on the product formation. For \(N\)-alkylbenzazepines 226, the reaction was proposed to occur via intermediate J', which is
hydrolyzed. Recyclization gives 1-aryl-tetrahydroisoquinolines 227. In case of N-acylbenzazepines 228, the reaction probably proceed via water attack at the aziridine moiety of intermediate K’ to yield 1-aryl-1-formyl-tetrahydroisoquinolines 229.

Scheme 47. Iron-promoted skeleton rearrangement of 226 and 227.
2.6 References


2 Iron-catalyzed C-N bond formations


Iron-catalyzed C-N bond formations


Iron-catalyzed C-N bond formations


Iron-catalyzed C-N bond formations


3 Objectives of this work

As demonstrated in the previous chapter, nitrogen-containing organic compounds are abundant in natural products and pharmaceuticals. The development of novel and efficient synthetic protocols for the synthesis of nitrogen-containing compounds continues to be of major importance in organic synthesis. In this respect, many catalytic reactions have proven to be efficient tools for the creation of C-N bonds. A significant disadvantage of many known precious metal catalysts are their toxicity and comparably high price. Therefore, the search for more economic and environmentally benign catalysts is still ongoing.

In the present dissertation the synthesis of nitrogen-containing compounds such as nitroolefins, oximes, propargyl amines, succinimides, and maleimides by applying iron catalysts was the main focus (Figure 7).

![Figure 7. The synthesized nitrogen-containing compounds.](image-url)

Clearly, in recent years it has been demonstrated that iron catalysis meets the criteria of sustainable metal chemistry. Thus, several model reactions to generate oximes, succinimides, and maleimides were studied in the presence of various iron catalysts. Furthermore, the optimized procedures were extended to the synthesis of a variety of interesting organic building blocks. In case of biologically active maleimides known natural products were also synthesized in a straightforward manner.

Another aim of this thesis were studies towards the synthesis of nitroolefins from nitric oxides and olefins under mild conditions. A comparison of nitration of olefins with NO and NaNO₂ was performed. Finally, we wanted to demonstrate the synthesis of propargyl amines from non-activated aliphatic amines and silylated alkynes.
4 Publications

4.1 A selective and practical synthesis of nitroolefins

DOI: 10.1002/adsc.200800509

Contributions
In this paper, I contributed to the writing process of the manuscript and was involved in discussions. My contribution as co-author of this paper is approximately 20%.
4.2 First iron-catalyzed synthesis of oximes from styrenes

DOI: 10.1039/b900326f

Contributions
In this paper, I planned, performed and analyzed all experiments. I wrote the manuscript, compiled the supporting information and was involved in discussions. My contribution as co-author of this paper is approximately 80%.
4.3 **α-Functionalization of non-activated aliphatic amines: ruthenium-catalyzed alkynylations and alkylations**


DOI: 10.1039/b924674f

**Contributions**

In this paper, I contributed to the writing process of the manuscript and was involved in discussions. My contribution as co-author of this paper is approximately 20%.
4.4 Efficient synthesis of biologically interesting 3,4-diaryl-substituted succinimides and maleimides: application of iron-catalyzed carbonylations


Contributions

In this paper, I planned, performed the experiments on the Sonogashira reaction and iron-catalyzed double carbonylation (Table 1, scheme 4) and the extension of the methodology for the synthesis of 3,4-bisindolylmaleimide (scheme 7). I wrote the manuscript, compiled the supporting information and was involved in discussions. My contribution as co-author of this paper is approximately 70%.
4.5 Iron-catalyzed carbonylation as a key step in the short and efficient syntheses of himanimide A and B

DOI: 10.1002/asia.201000384

Contributions
In this paper, I planned, performed and analyzed all experiments. I wrote the manuscript, compiled the supporting information and was involved in discussions. My contribution as co-author of this paper is approximately 75%.
5 Summary

We have successfully developed novel methods for the synthesis of nitrogen-containing compounds such as nitroolefins, oximes, propargyl amines, succinimides and maleimides. In most cases, the reaction could be performed under iron catalysis.

In order to use nitric oxide (NO) as the nitrogen source in nitration reaction, the reaction of NO with olefins has been investigated. The direct nitration of a range of olefins underwent successfully at room temperature leading to the formation of nitroolefins in high regioselectivity and good yields without the need of catalyst (Scheme 48). For details, see Publication 4.1, *Adv. Synth. Catal.* 2008, 350, 2493-2497.

![Scheme 48. Nitration of various olefins.](image)

*tert*-Butyl nitrite, which was known as efficient NO equivalent, can also be used for the synthesis of oximes from styrenes by using a biomimetic iron phthalocyanine complex catalyst and readily available reductant (NaBH₄). For details, see Publication 4.2, *Chem. Commun.* 2009, 1990-1992.

We demonstrated a novel synthetic route for the preparation of propargyl amines via the reaction between aliphatic amines and silylated alkynes in the presence of Shvo catalyst (Scheme 49). Several metal complexes including iron and ruthenium complexes have been studied. However, only the Shvo complex could catalyze the reaction to produce propargyl amines. The transformation probably involved a dehydrogenation-alkynylation sequence. For details, see Publication 4.3, *Chem. Commun.* 2010, 46, 1956-1958.
Encouraged by our experience in iron-catalyzed carbonylation of alkynes with ammonia or amines, we decided to study further the carbonylation reaction of various unsymmetrical 1,2-diarylalkynes, which was prepared by the palladium-catalyzed Sonogashira reaction (Scheme 50). Thus, 3,4-diaryl-substituted succinimides have been synthesized in moderate to high yield and converted to the corresponding maleimides via dehydrogenation reaction. Based on this work, we demonstrated our synthetic method in the synthesis of arcyriarubin derivative, himanimide A and B. For details, see Publication 4.4, *Chem. Eur. J.* 2010, 16, 9606-9615 and Publication 4.5, *Chem. Asian. J.* 2010, 5, 2173-2176.
Selbstständigkeitserklärung

Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, 11. August 2010

Sasuree Prateeptongkum