Iron-catalyzed C-N bond formations

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University of Rostock

Abstract

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.

Die vorliegene Dissertation beschäftigt sich hauptsächlich mit der Entwicklung und der Anwendung von eisenkatalysierten Reaktionen für die Synthese von stickstoffhaltigen organischen Verbindungen. So gelang es, Oxime in einer neuartigen eisenkatalysierten Nitrosierung von Olefinen mit *tert*-Butylnitrit und Natriumborhydrid herzustellen. Succinimide und Maleimide konnten unter Verwendung von eisenkatalysierten Carbonylierungen interner Alkine mit Ammoniak als Schlüsselschitt generiert werden. Diese sehr effiziente Methode wurde mit interessanten organischen Bausteinen auf die Synthese von Naturstoffen übertragen. Darüberhinaus beschreibt diese Dissertation die Entwicklung eines effizienten Syntheseprotokolls für die Darstellung verschiedener Nitroolefine. Zusätzlich wird auch die Synthese von Propargylaminen unter Verwendung von Shvo-katalysierten Alkinierungsreaktionen vorgestellt.

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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	η^5-Cyclopentadienyl
DCE	1,2-dichloroethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
$(DHQD)_2Pyr$	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)

Pc	Phthalocyanine
Pd/C	Palladium on carbon
PG	Protecting group
Ph	Phenyl
Pip	Piperidine
i-Pr	*iso*-Propyl
n-Pr	*n*-Propyl
R	Organic group
rac	Racemic
rt	Room temperature
Ses	2-Trimethylsilylethanesulfonyl
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPP	Tetraphenylporphyrin
Ts	Toluene-*p*-sulfonyl

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.

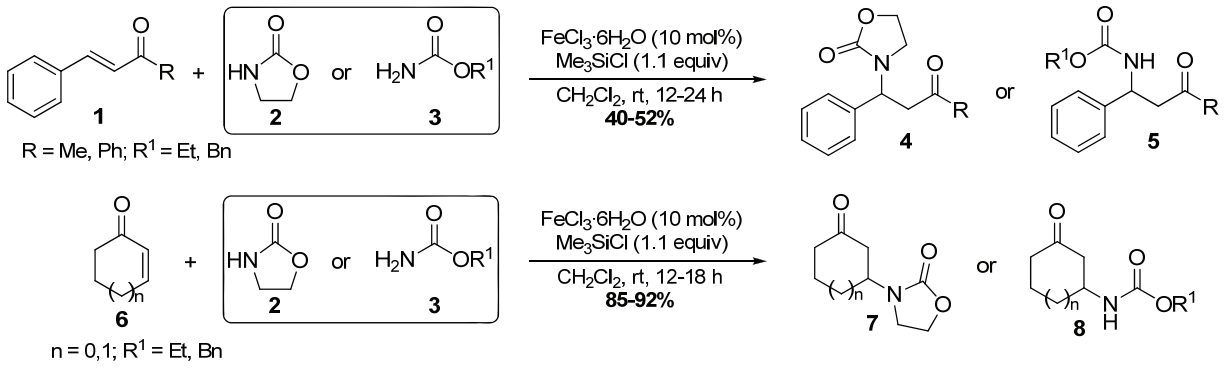
2 Iron-catalyzed C-N bond formations

2.1 Addition reactions

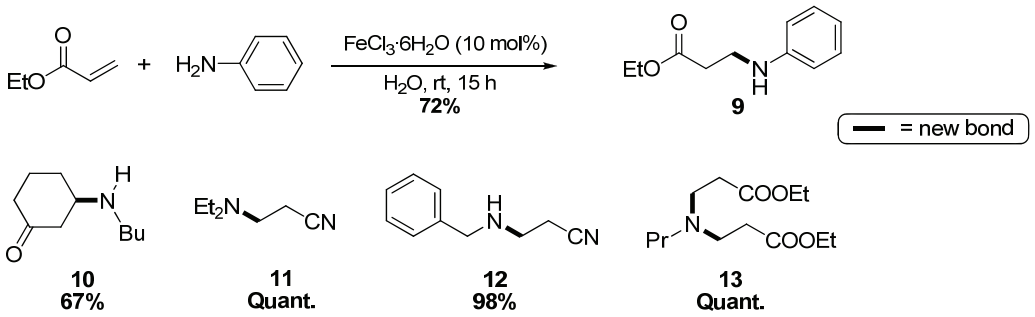
2.1.1 Aza-Michael additions

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.[3] In the past few years, a large number of alternative procedures have been reported using $Cu(OAc)_2 \cdot H_2O$,[4] $LiClO_4$,[5] $Cu(OTf)_2$,[6] $Bi(OTf)_3$,[7] $Bi(NO)_3$,[8] $CeCl_3 \cdot 7H_2O/NaI$,[9] $InCl_3$,[10] $Ln(OTf)_3$.[11]

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.[12] Moreover, $FeCl_3$ has also been proven to be effective for the conjugate addition of secondary amines to the weak acceptor α-acetamidoacrylate.[13] 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 $FeCl_3 \cdot 6H_2O$ 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).[14]



Scheme 1. Aza-Michael reaction of enones with carbamates.

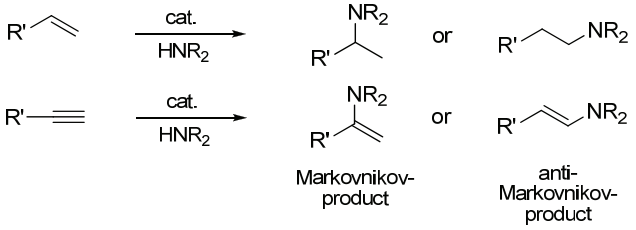


Scheme 2. Aza-Michael reaction of α,β-unsaturated electrophiles with amines.

More attractive catalytic systems for aza-Michael addition of ethyl acrylate and electrophilic α,β-unsaturated compounds with amines were also reported (Scheme 2).[15] Among several transition-metal-based Lewis acid catalysts, $FeCl_3 \cdot 6H_2O$ 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**.

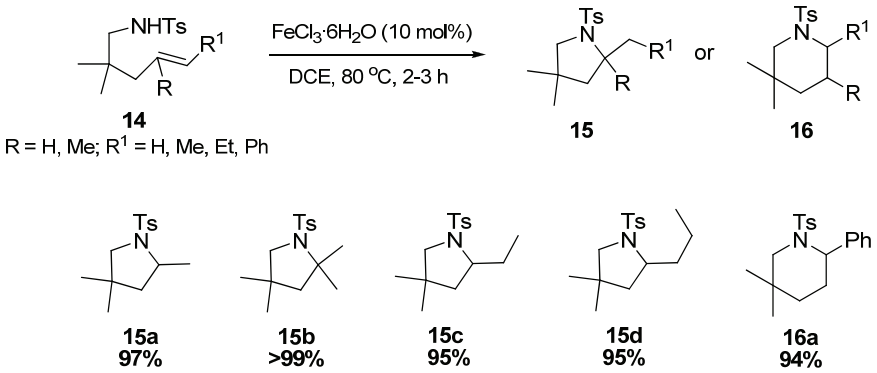
2.1.2 Hydroaminations of non-activated alkenes and alkynes

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).[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.



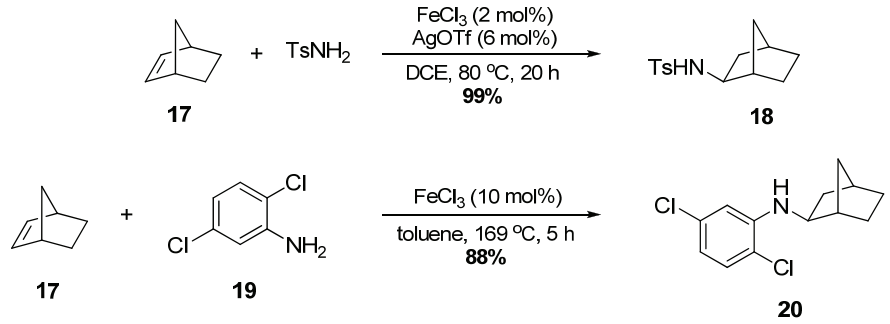
Scheme 3. Hydroamination of alkenes and alkynes.

The first report of intramolecular iron-catalyzed hydroamination of unactivated olefins **14** was published by Takaki and co-workers in 2006.[17] Among the transition-metal catalysts tested, e.g. $FeCl_3$, $FeCl_3{\cdot}6H_2O$, $FeCl_2{\cdot}4H_2O$, $Fe(NO_3)_3$, $Fe_2(SO_4)_3$, $Fe(acac)_3$, $Cu(OTf)_2$, AgOTf, $CoCl_2$, $NiCl_2$, $CuCl_2$ and $ZnCl_2$, $FeCl_3{\cdot}6H_2O$ 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 **15** were formed preferentially compared to the 6-endo-trig cyclization product **16**.



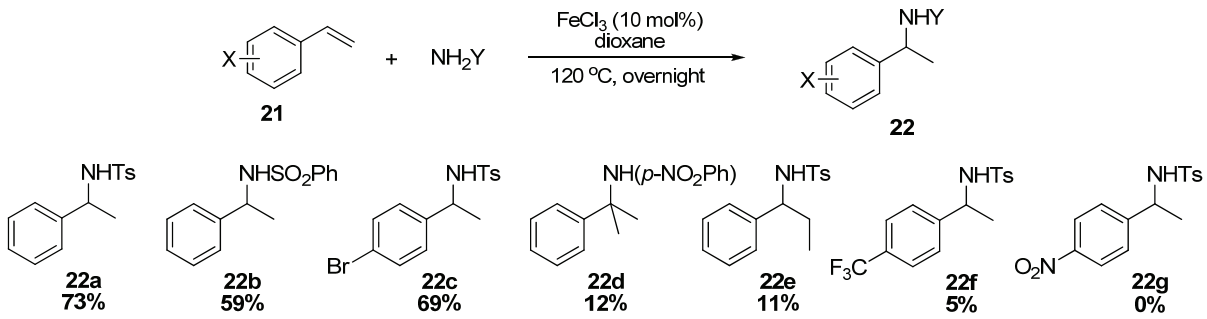
Scheme 4. Intramolecular hydroamination of aminoolefins **14**.

In 2007, hydroamination of norbornene (**17**) with amines has been reported by Takaki *et al*. and Li *et al*.[18] Here, the cationic catalyst, $Fe(OTf)_3$ derived from $FeCl_3$ and AgOTf, was found to produce the active catalyst for the intermolecular hydroamination of **17** and $TsNH_2$[18a] while the use of $FeCl_3$ alone for the addition of 2,5-dichloroaniline (**19**) to **17** needed more severe conditions.[18b]

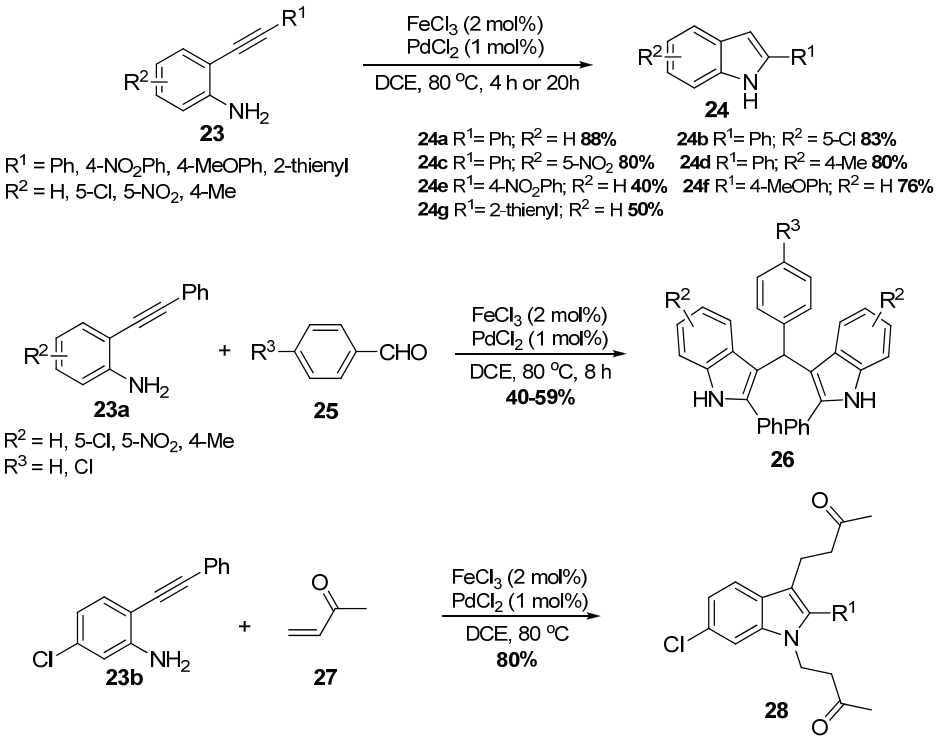


Scheme 5. Intermolecular hydroamination of norbornene (**17**) and amines.

Recently, Prim and Campagne *et al*. published the intermolecular $FeCl_3$-catalyzed hydroamination of styrenes (Scheme 6) and the use of a new catalytic combination ($FeCl_3$:$PdCl_2$ = 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 $FeCl_3$ 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]



Scheme 6. Intermolecular hydroamination of styrenes **21** and amines.



Scheme 7. Synthesis of indoles and bis(indolyl)methanes *via* hydroamination.

Intramolecular hydroamination of alkynylanilines **23** to give indoles have been reported in the presence of low loadings of the bimetallic catalyst system ($FeCl_2$:$PdCl_2$ = 2:1 mol%) in open-air flasks. It is believed that O_2 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]

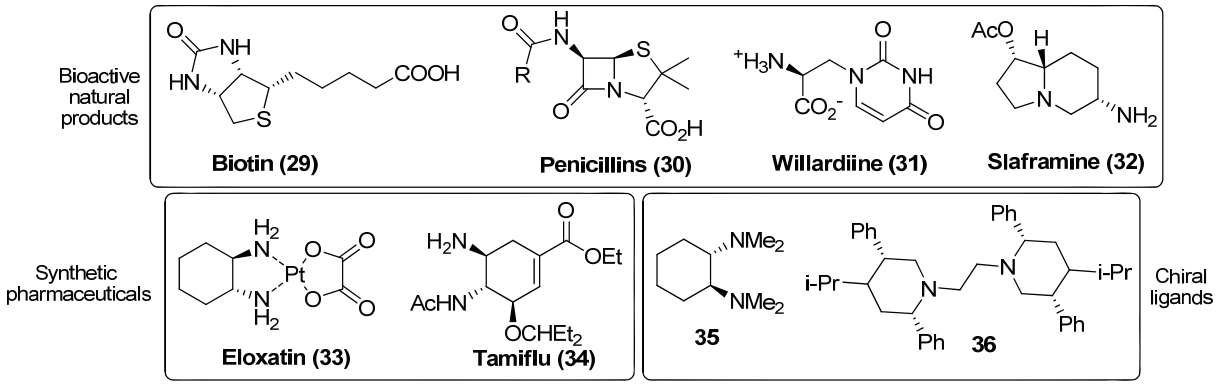
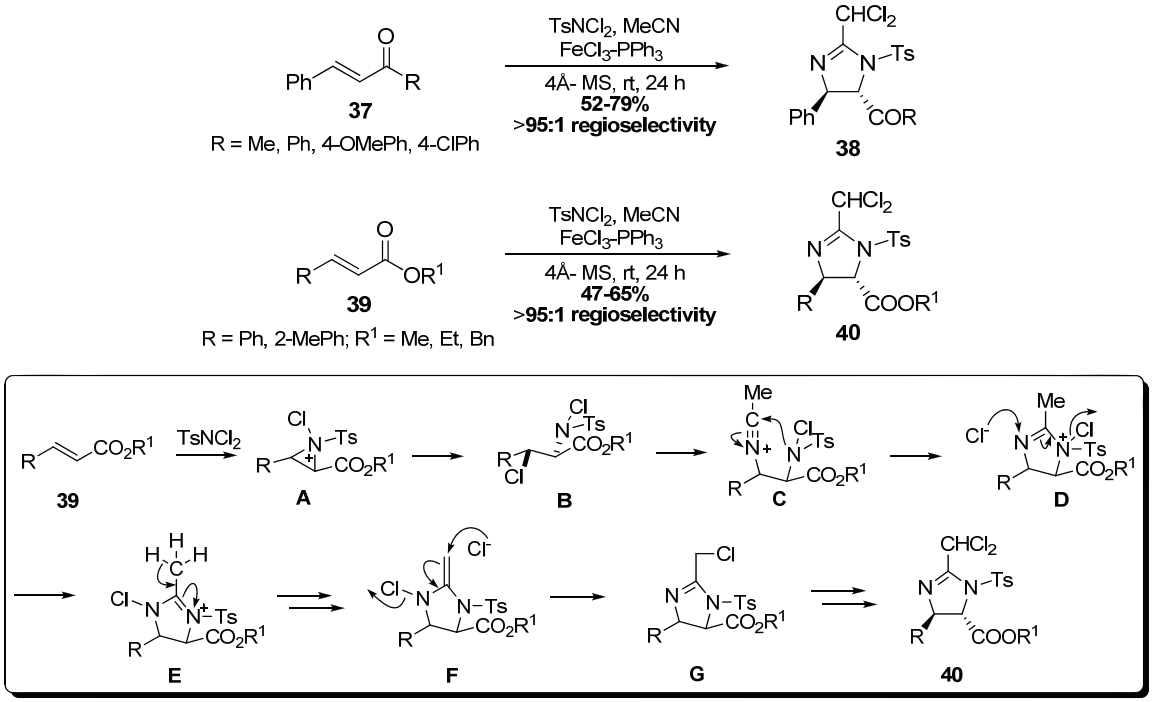


Figure 1. Examples of 1,2-diamines in natural products, pharmaceuticals and asymmetric organic synthesis.

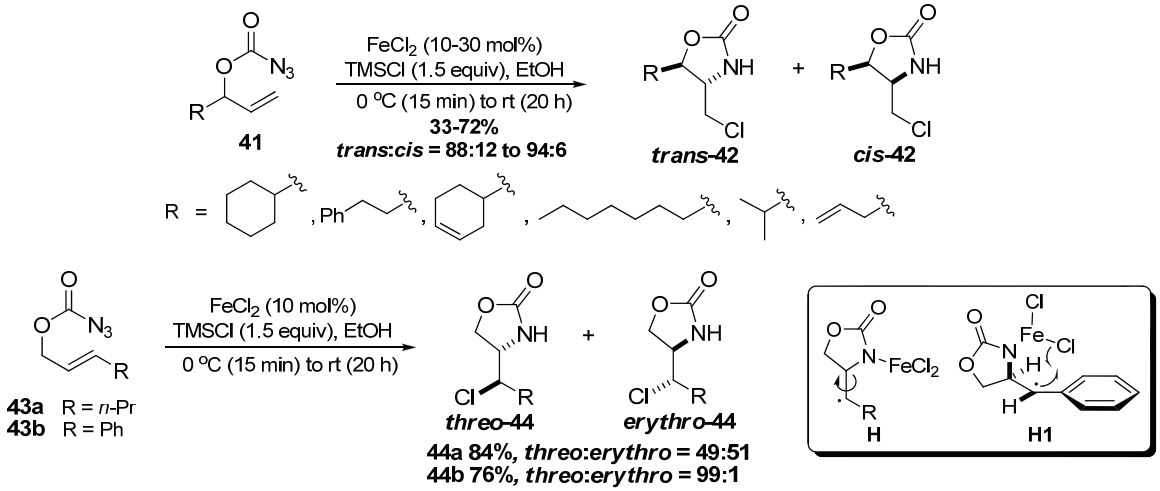
An iron-catalyzed 1,2-diamination reaction of α,β-unsaturated ketones **37** and esters **39** has been reported by Li *et al*. in 2002, which led to the formation of imidazoline derivatives **38** and **40**, respectively (Scheme 8).[22] The electrophilic diamination of electron-deficient alkenes by 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.[23] The proposed mechanism involves the formation of aziridinium intermediate **A**, which is further attacked at the β-position by chlorine anion to generate *N*-chloro haloamine intermediate **B**. Subsequent S_N2 displacement with MeCN affords a nitrinium intermediate **C**. These two steps are responsible for the high stereoselectivity.[23]



Scheme 8. Diamination of α,β-unsaturated ketones **37** and esters **39**.

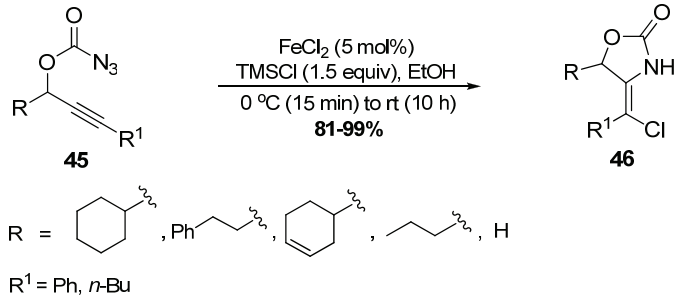
2.1.4 Aminochlorinations

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**.



Scheme 9. Intramolecular aminochlorination of 2-alkenyloxycarbonyl azides **41** and **43**.

Propargyloxycarbonyl azides **45** underwent dediazotation under similar conditions to give highly *syn*-selective oxazolidinones **46** in excellent yields (Scheme 10).[24,26]



Scheme 10. Intramolecular aminochlorination of propargyloxycarbonyl azides **45**.

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).[27] 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.[28] In addition, palladium[29] and copper[30] catalysts have also been shown to be effective catalysts for this addition reaction.

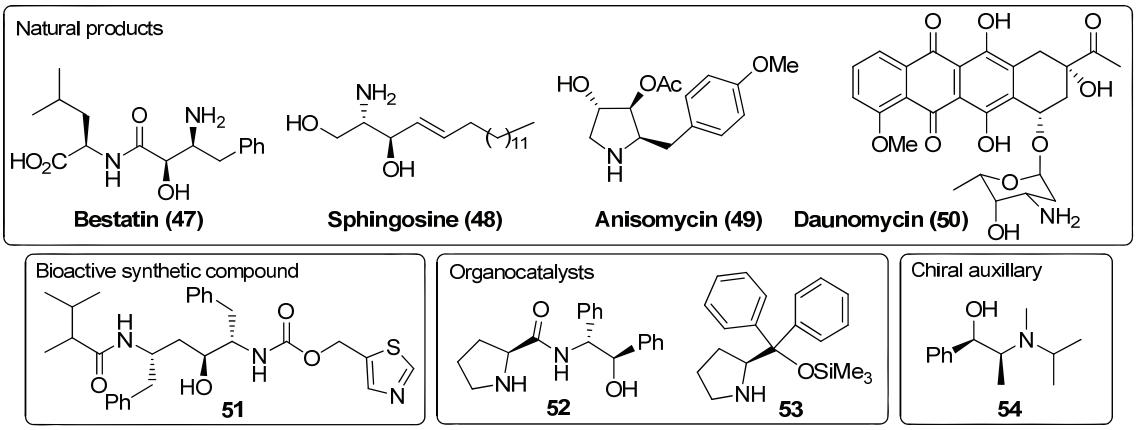
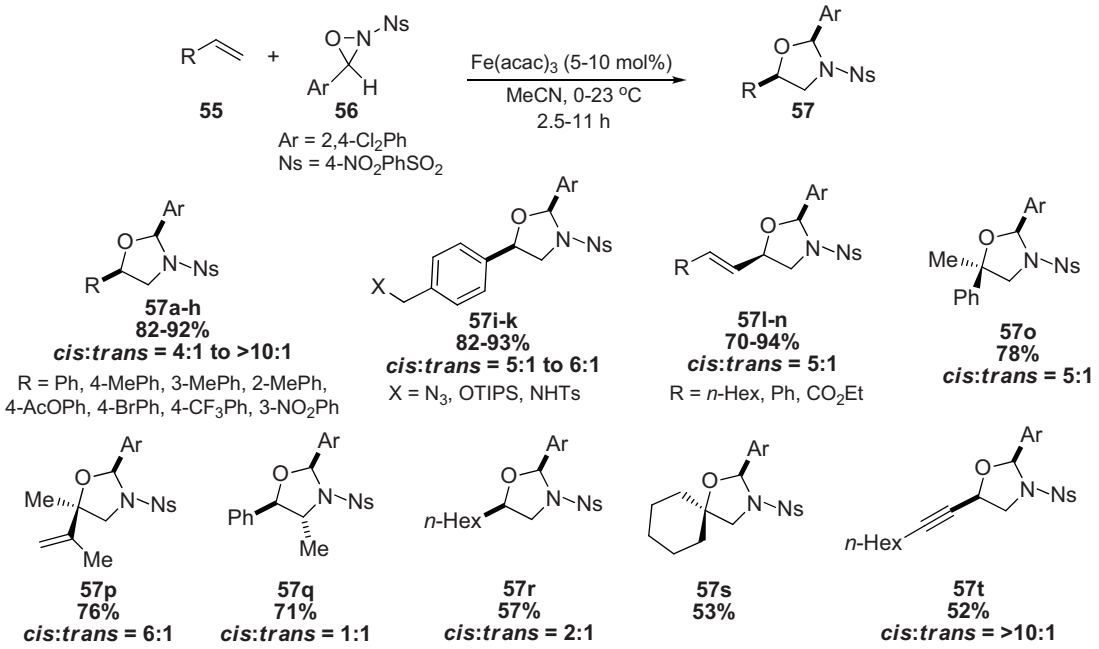


Figure 2. Examples of 1,2-aminoalcohols in natural products, bioactive synthetic compounds, organocatalysts and chiral auxillaries.

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 α– and β–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 (±)-octapamine (see chapter 2.4.2).



Scheme 11. Aminohydroxylation catalyzed by iron(III) complexes.

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]

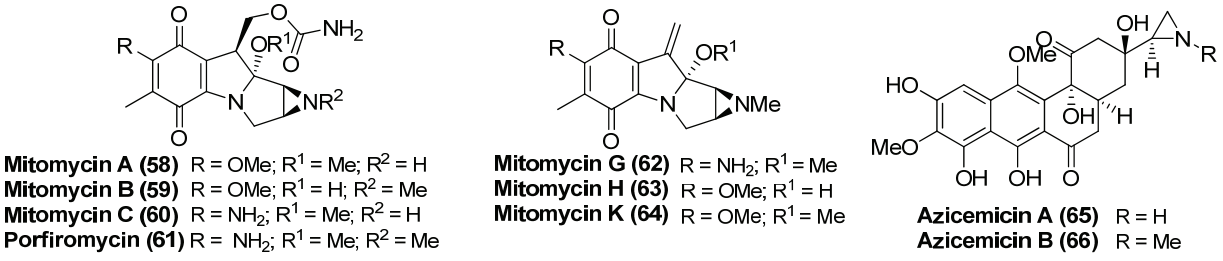
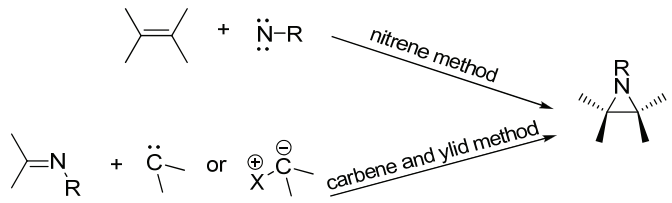
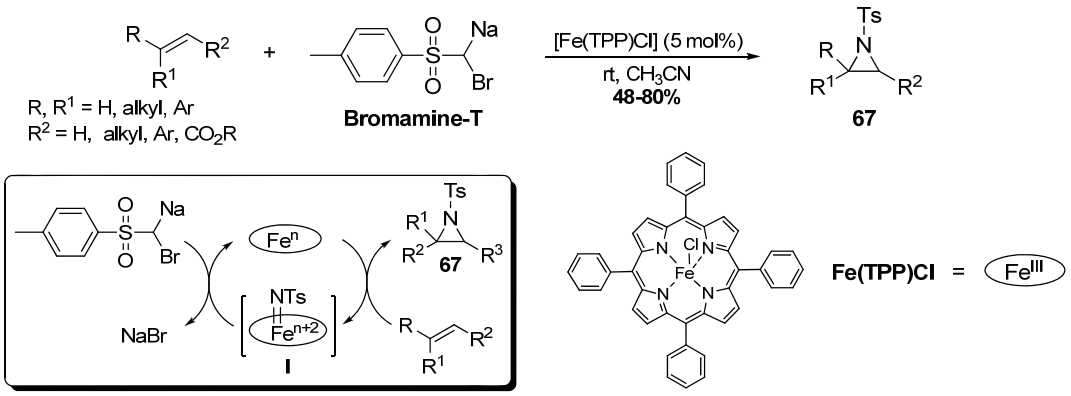


Figure 3. Examples of natural products containing aziridines.



Scheme 12. Synthetic routes to aziridines.

Iron(III) porphyrin and iron(IV) corrole complexes were recognized to be effective catalysts for nitrene transfer reactions.[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.[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 by-product. Therefore, different nitrene sources have been investigated. For example, Zhang *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 α,β-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).[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.[37] These catalytic aziridination are assumed to proceed *via* an iron-nitrene intermediate **I** (Scheme 13).



Scheme 13. Aziridination catalyzed by iron(III) porphyrin complex.

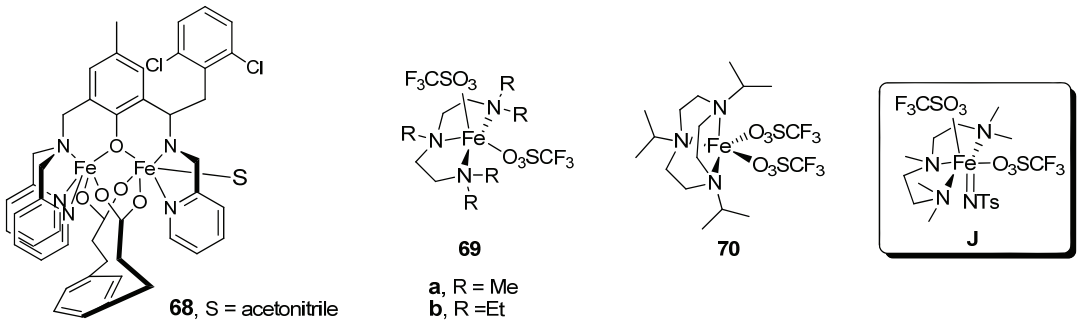
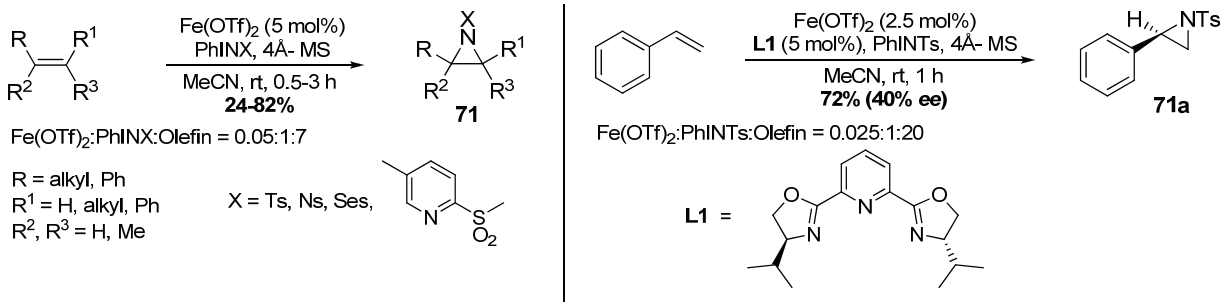


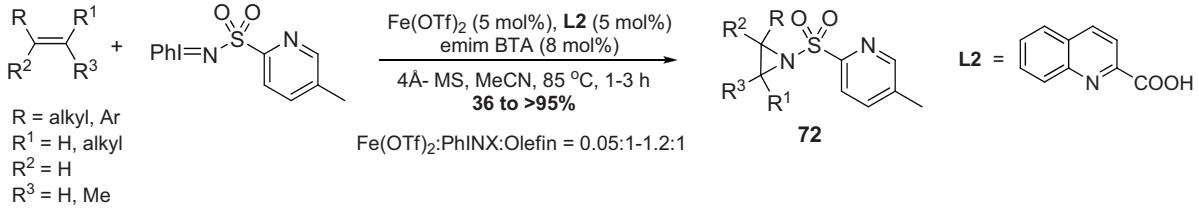
Figure 4. Non-heme iron complexes for aziridination.

The use of non-heme iron complexes in catalytic aziridination has been studied by Latour *et al*.[38] and Halfen *et al* (Figure 4).[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.[38] The mononuclear non-heme iron(II) complexes **69**-**70** have been employed as the olefin aziridination catalysts by Halfen and co-workers.[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**.[39a]

Bolm and co-workers described iron(II) triflate-catalyzed aziridination reactions in the presence of preformed iminoiodinanes $PhINSO_2Ar$ 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).[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).[41]

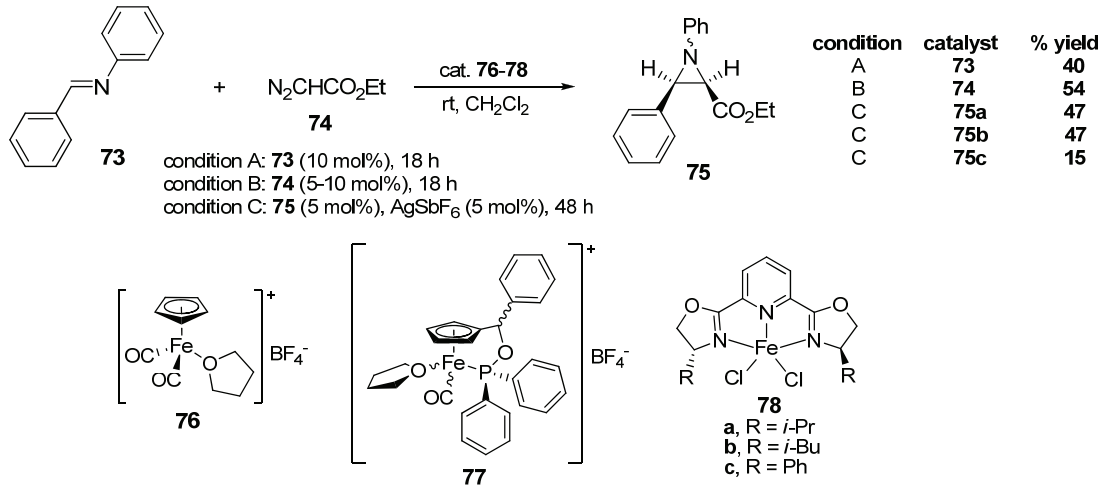


Scheme 14. Aziridination catalyzed by iron(II) triflate.



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

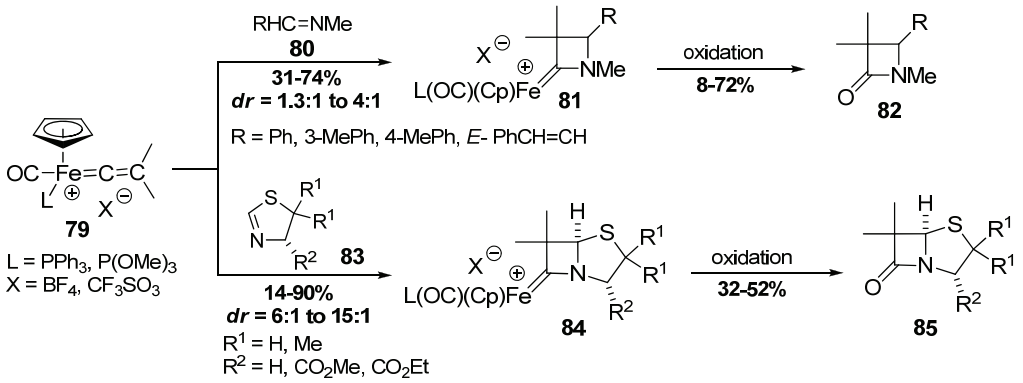
Iron-based Lewis acid catalysts, $[(\eta^5\text{-}C_5H_5)(CO)_2Fe(THF)]^+[BF_4]^-$ (**76**) and $[(\eta^5\text{: }\eta^1\text{-}C_5H_4CH(Ph)OPPh_2)Fe(CO)(THF)]^+[BF_4]^-$ (**77**), and iron-pybox complexes (**78**) were employed in the reaction between imine **73** and ethyl diazoacetate (**74**) by 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

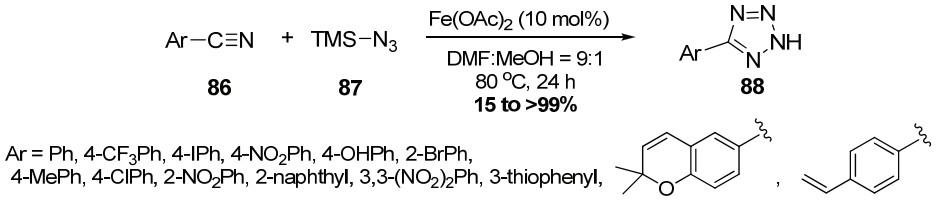
Formal [2+2]-cycloaddition reaction of iron(II) vinylidene complexes was reported by Barrett and co-workers.[44] Reaction of cationic iron(II) vinylidenes **79** with imines **80** and thiazolines **83** provided the corresponding azetidinylidene complexes **81** and **84.** Subsequent oxidation of these complexes led to mono- or bicyclic β-lactams **82** and **85** (Scheme 17).



Scheme 17. Iron(II) vinylidenes in β-lactam synthesis.

2.2.3 [2+3]-Cycloadditions

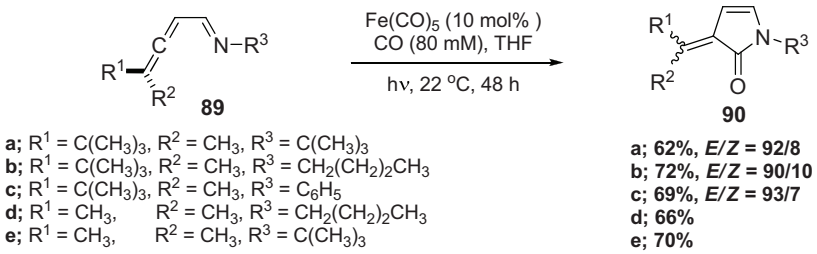
The [2+3]-cycloaddition of nitriles **86** and trimethylsilyl azide (**87**) proceed in the presence of a catalytic amount of $Fe(OAc)_2$ in a 9:1 mixture of DMF and MeOH at 80 °C (Scheme 18).[45] It should be noted that the purity of the iron source affected the yield of the tetrazole products. Generally, 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.



Scheme 18. Formal [2+3] cycloaddition to 5-substituted 1*H*-tetrazoles **88**.

2.2.4 [4+1]-Cycloadditions

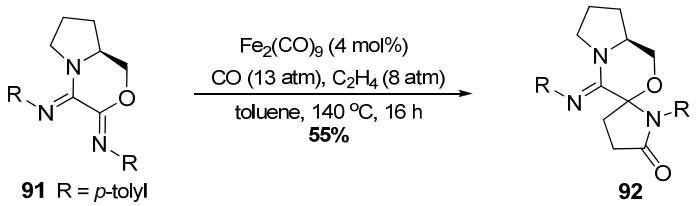
The construction of pyrrolinones **90** *via* [4+1]-Cycloaddition of allenyl imines **89** and CO employing $Fe(CO)_5$ as a catalyst have been described by Eaton *et al*. (Scheme 19).[46] The iron-catalyzed photochemical reaction proceeded under mild condition (22 °C, 80 mM CO) with fluorescent light providing good yields of **90**. High stereoselectivity is achieved when the terminal allene groups are *tert*-butyl and methyl.



Scheme 19. Formal [4+1] cycloaddition to 3-alkylidene-4-pyrrolin-2-ones **90**.

2.2.5 [2+2+1]-Cycloadditions

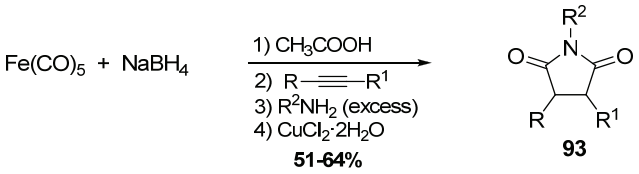
Catalytic intermolecular hetero-Pauson-Khand-type reactions, a formal [2+2+1] cycloaddition reaction, between 1,4-diazabutadienes, carbon monoxide and ethylene to give pyrrolidin-2-one **92** has been demonstrated by Imhof and Anders *et al*. (Scheme 20).[47] The reaction proceeded with complete regioselectivity 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.



Scheme 20. Formal [2+2+1] cycloaddition to spirolactams **92**.

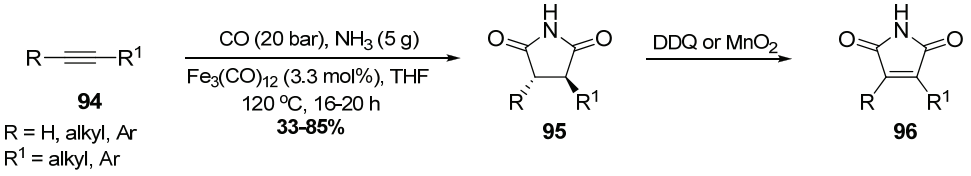
2.2.6 [2+1+1+1]-Cycloadditions

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 $CuCl_2 \cdot 2H_2O$ 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.

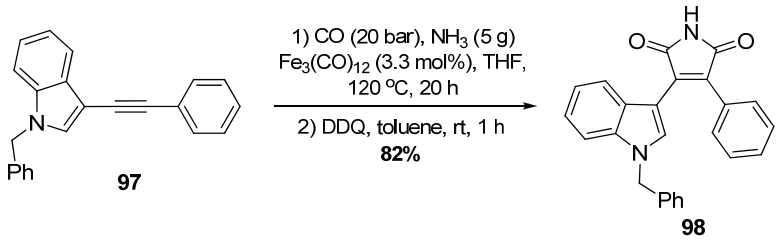


Scheme 21. The synthesis of succinimides **93** using iron carbonyl complexes.

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).

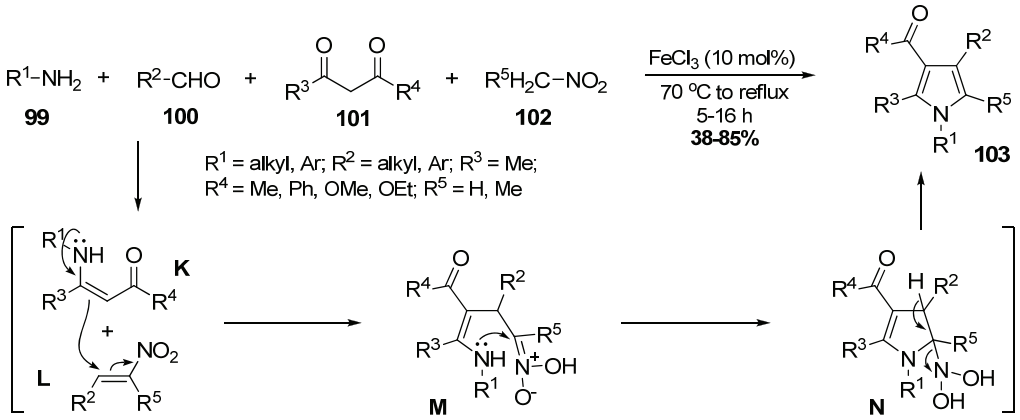


Scheme 22. Formal [2+1+1+1] cycloaddition to succinimides **95**.



Scheme 23. One-pot synthesis of maleimide **98**.

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).[50] 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.

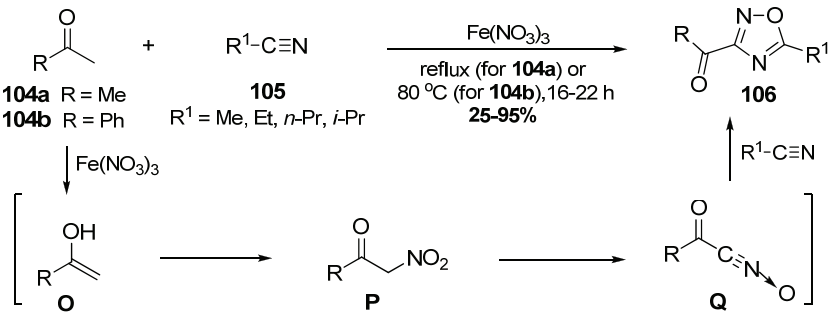


Scheme 24. One-pot synthesis of highly functionalized pyrroles **103**.

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).[51] 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-oxadiazole **106** in low to excellent yields depending on the stability of the nitrile oxides and the reactivity of nitriles in 1,3-dipolar cycloaddition.

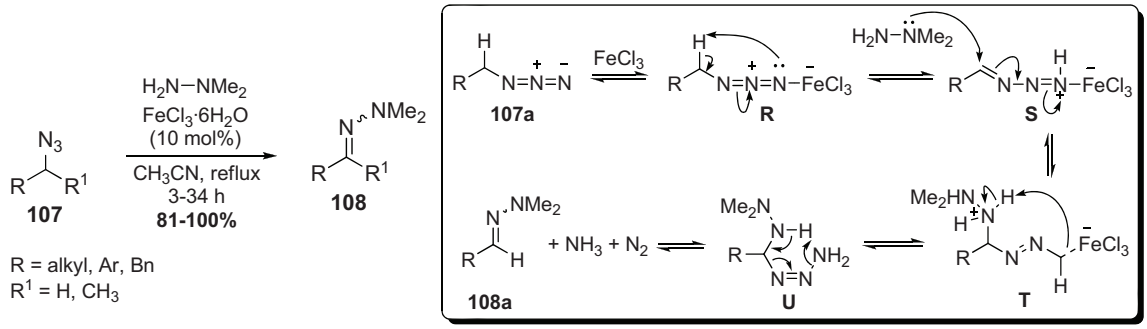


Scheme 25. One-pot synthesis of 1,2,4-oxadiazoles **106**.

2.3 Substitution reactions

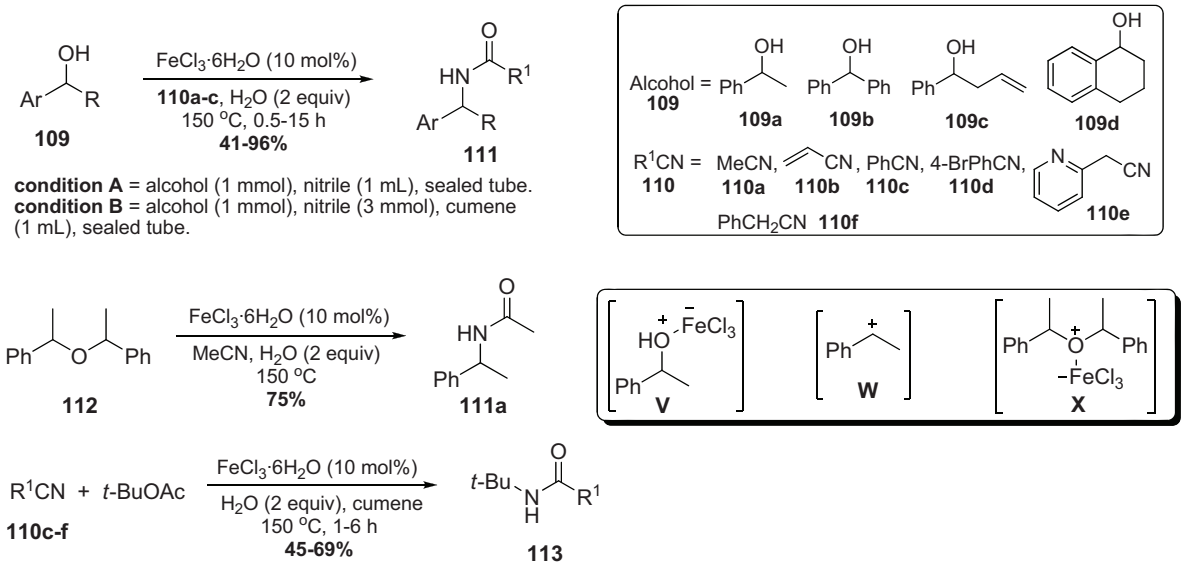
2.3.1 Nucleophilic substitution of non-activated C-X bonds

The substitution reaction of azides **107** by *N*,*N*-dimethylhydazine in the presence of catalytic amounts of $FeCl_3 \cdot 6H_2O$ led to *N*,*N*-dimethylhydrazone **108** in high to excellent yields (Scheme 26).[52] The reaction was postulated to proceed *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**.



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,[53] Nafion[54] and bismuth triflate.[55] Recently, the groups of Reymond and Cossy reported that Ritter reactions are also catalyzed by $FeCl_3 \cdot 6H_2O$ (10 mol%) (Scheme 27).[56] 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 $FeCl_3 \cdot 6H_2O$ at 150 °C. The ether formation from benzylic alcohol proceeded in the presence of $FeCl_3$[57] or $Fe(NO_3)_3$.[58] 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.

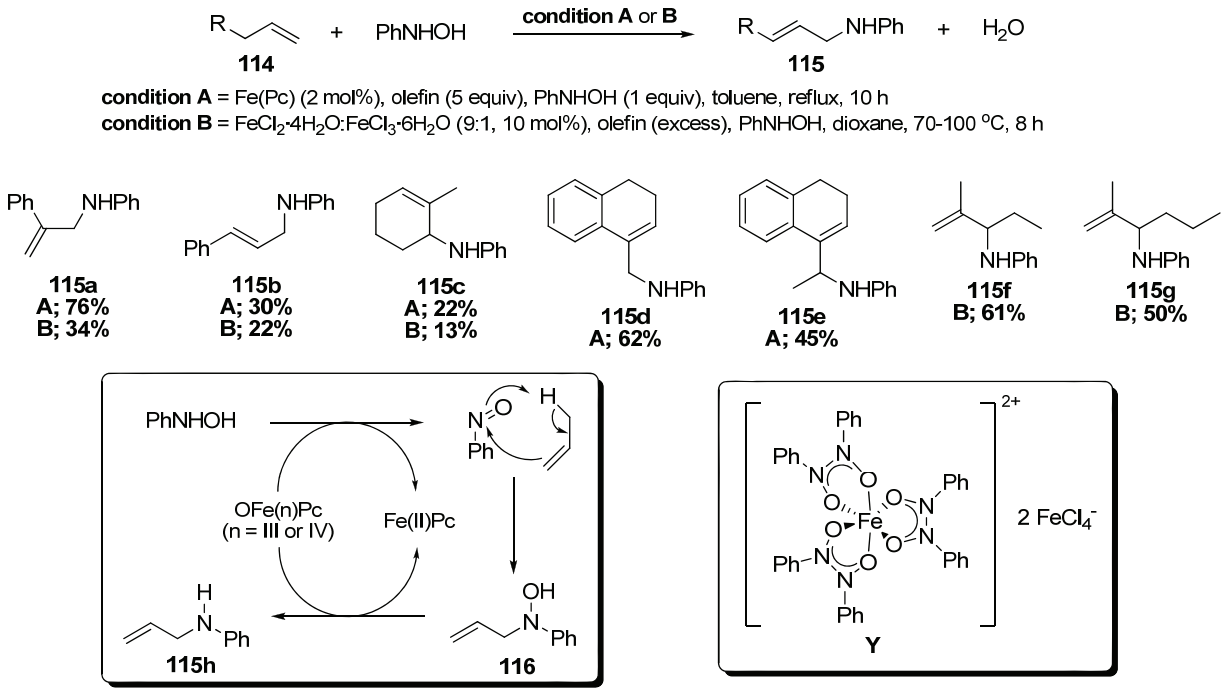


Scheme 27. Iron-catalyzed Ritter reaction.

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,[59] α- and β-amino acids, *etc*.[60] Several transition metal-catalyzed allylic amination reaction[61] using Pd, Ir,

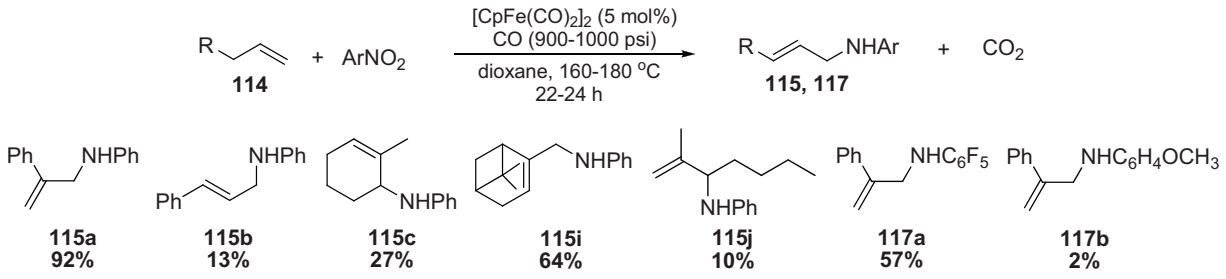
Ru and Rh as metal sources have been investigated.[62] Iron catalysis of this reaction has also been developed. In 1994, Jørgensen *et al*.[63] and Nicholas *et al*.[64] published the preparation of allylamines from alkenes and phenylhydroxylamine by using iron phthalocyanine [Fe(Pc); condition A] and/or iron salts (condition B) as the catalysts (Scheme 28).



Scheme 28. Allylic amination of phenylhydroxylamine with alkenes.

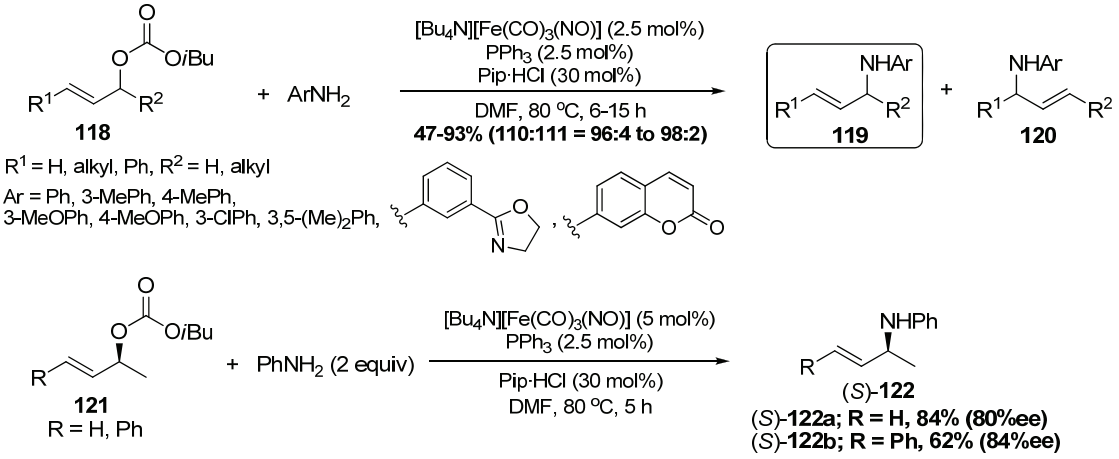
Under conditions A, only aromatic alkenes were efficiently converted into the corresponding allylamines (**115a**, **115d**, **115e**). In contrast, aliphatic internal alkenes gave significantly better yields of products (**115f**, **115g**) under the conditions B. The allylic amination reactions were found to proceed *via* different mechanisms depending on the catalytic systems chosen. From mechanistic studies of this reaction catalyzed by Fe(Pc),[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.[66]

Nicholas and co-workers have extended these studies by using more readily available amination agents, e.g. nitroarenes, instead of phenylhydroxylamine (Scheme 29).[67] The reaction of nitroarenes and alkenes took place in the presence of carbon monoxide using $[CpFe(CO_2)]_2$ 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.[68]



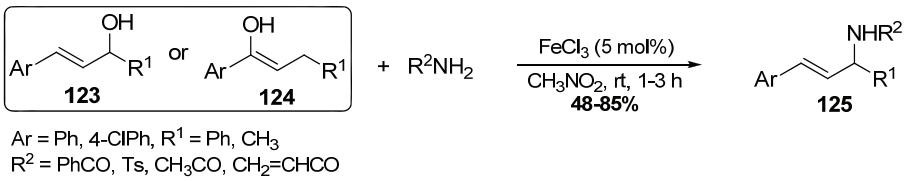
Scheme 29. Allylic amination of nitroaromatics with alkenes.

Plietker developed a catalytic system for allylic amination reactions of allyl carbonates **118** with primary anilines, which were catalyzed by $[Bu_4N][Fe(CO)_3(NO)]$ (Scheme 30).[69] 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 σ-allyl metal intermediate in the proposed mechanism.[70]



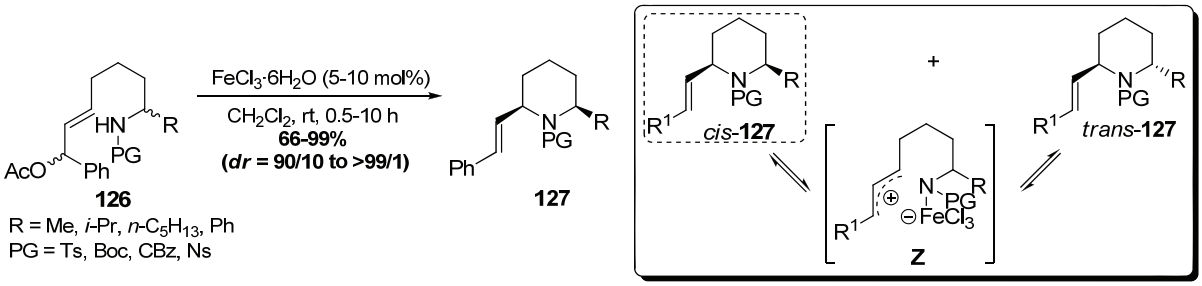
Scheme 30. Allylic amination of anilines with allyl carbonates **118** and **121**.

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 $FeCl_3$ (Scheme 31).[71] 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* S_N1 mechanism.



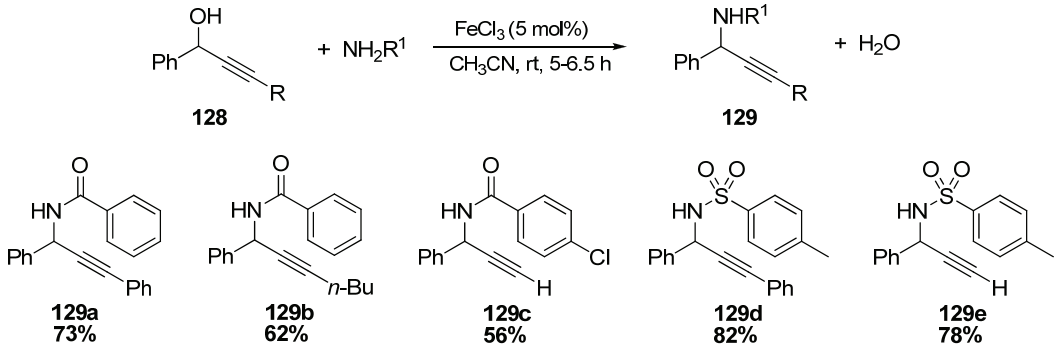
Scheme 31. Allylic amination of amides with allylic alcohols **123** and **124**.

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).[72] 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 $FeCl_3 \cdot 6H_2O$-catalyzed epimerization to the thermodynamically more stable *cis*-isomer *via* zwitterionic intermediate **Z**.



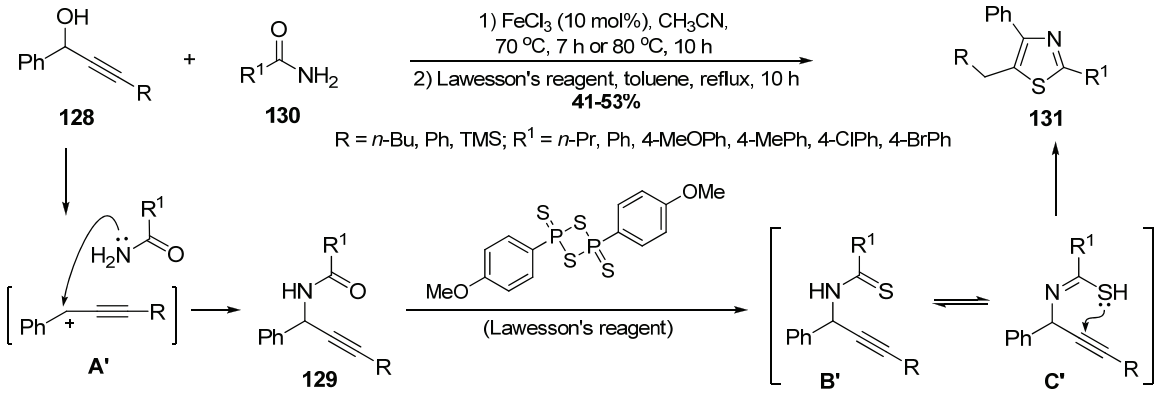
Scheme 32. Intramolecular allylic amination of amino allylic alcohols **126**.

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 $[Co_2(CO)_8]$ 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 *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 $FeCl_3$ (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 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.



Scheme 34. One-pot synthesis of substituted thiazoles **131**.

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.

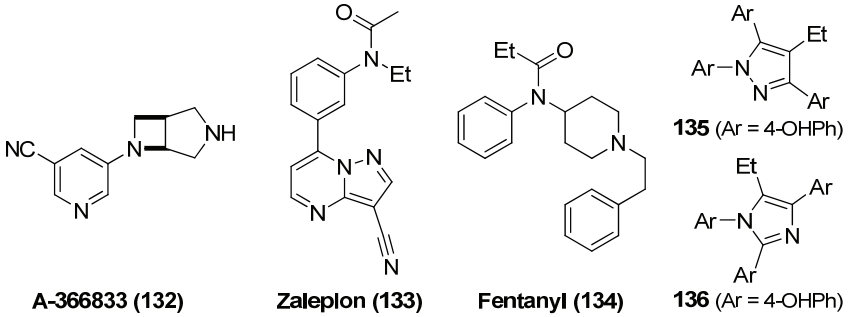
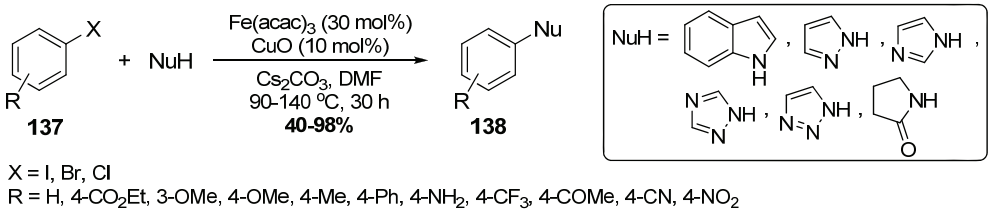


Figure 5. Representative biologically active arylamines , arylamides, arylpyrazoles, and arylimidazoles.

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).[85] Coupling reactions of aryl iodides and few aryl bromides were performed under mild conditions (90 ^{o}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 ^{o}C or 140 ^{o}C) were necessary. As an advantage of this catalytic system no side-product was formed during the catalysis.

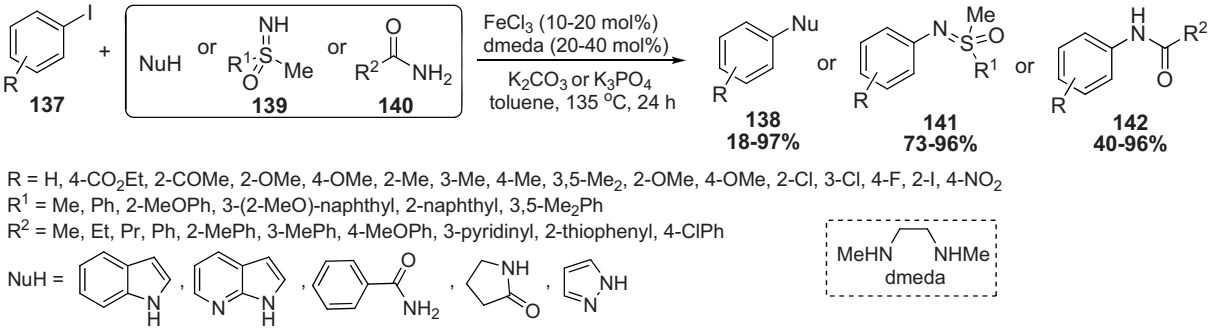


Scheme 35. *N*-Arylation of aryl halides **137** with nitrogen nucleophiles.

Another iron/copper catalytic system for the cross-coupling reaction of *N*-heterocycles with aryltrimethoxysilanes or vinyltrimethoxysilane was developed by Li *et al*..[86] Here, *N*-arylations of imidazoles and triazoles were carried out by using $FeCl_3$/Cu and TBAF as base under air atmosphere in the absence of solvents to afford the corresponding products in moderate to excellent yields.

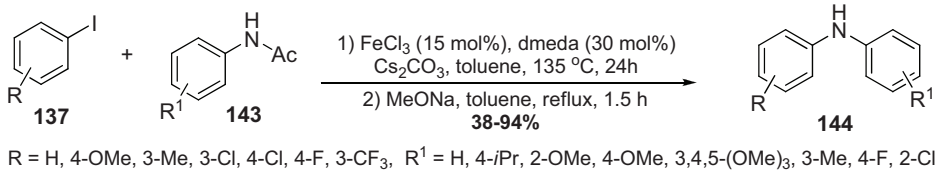
Shortly thereafter, Bolm *et al*. published the first genuine iron-catalyzed *N*-arylation.[87] The active catalytic system consisted of $FeCl_3$ (10-20 mol%), dmeda (20-40 mol%) as chelating ligand and base (K_2CO_3, K_3PO_4 or Cs_2CO_3) without the need of added copper. Temperature and solvent selection 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).



Scheme 36. *N*-Arylation of aryl iodides **137** with sulfoximine **139** or amides **140**.

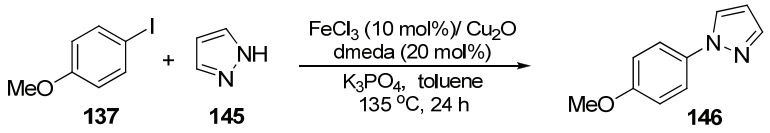
Acetanilides were also suitable substrates under slightly modified condition (using Cs_2CO_3 as the base instead of K_2CO_3 or K_3PO_4) (Scheme 37).[90] This protocol allowed the preparation of a range of diarylamines **144** in a one-pot procedure by iron-catalyzed *N*-arylation of aryl iodides **137** 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).[91] *N*-Arylation reaction of pyrrazole with 4-iodoanisole with >99.99% $FeCl_3$ gave lower yield than that with >98% $FeCl_3$. The better yield is observed when 5-10 ppm Cu_2O was used together with >99.99% $FeCl_3$. The authors suggested that trace amount of other metals, especially copper, are responsible for the catalytic activity.

Table 1. *N*-Arylation reaction of pyrrazole catalyzed by different $FeCl_3$/Cu_2O.



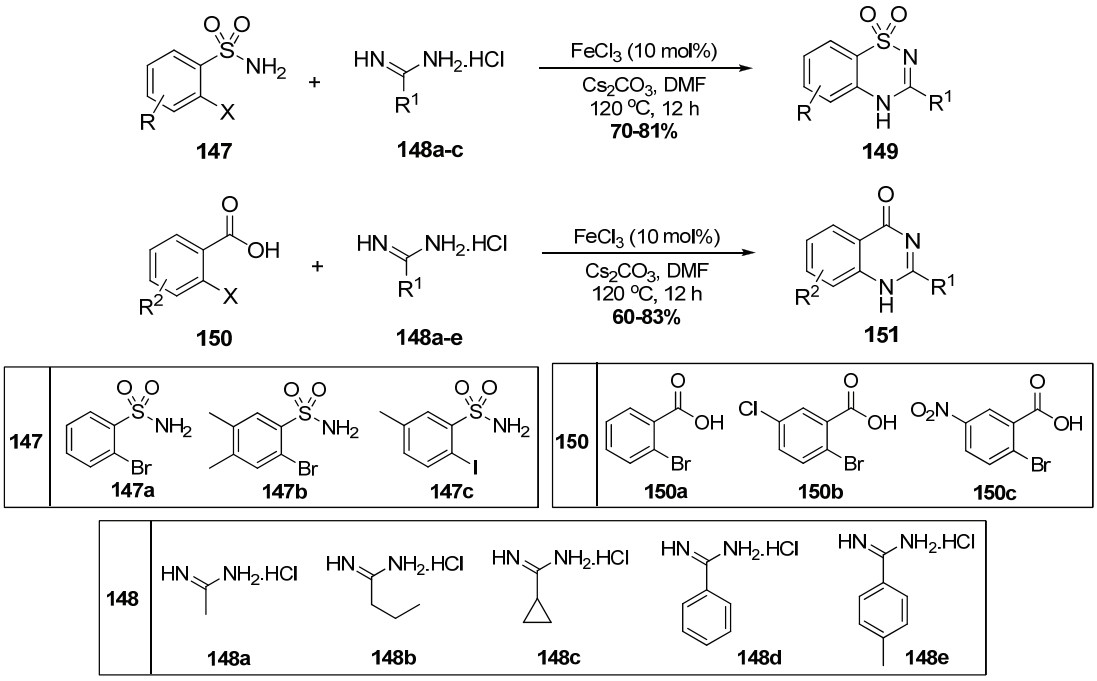
$FeCl_3$	Cu_2O	Yield [%] (GC)
>98% (Merck)	-	87
>98% (Aldrich)	-	26
>99.99% (Aldrich)	-	9
>99.99% (Aldrich)	5 ppm Cu_2O	78
>99.99% (Aldrich)	10 ppm Cu_2O	79
-	5 ppm Cu_2O	77
-	5 ppm Cu_2O	23[a]

[a] in the absence of ligand

Liu and co-workers have developed a novel iron catalyst system for C-N cross-coupling reactions based on the use of Fe_2O_3 (10 mol%), L-proline (20 mol%), and NaO*t*Bu (2 equiv) in DMSO at 135 °C for 24 h.[92] A variety of nitrogen-containing compounds such as aliphatic primary amines, aliphatic secondary amines, benzylamine, aniline, and *N*-heterocycles (pyrazole, indole and benzoimidazole) were coupled with iodobenzene but only aliphatic primary amines

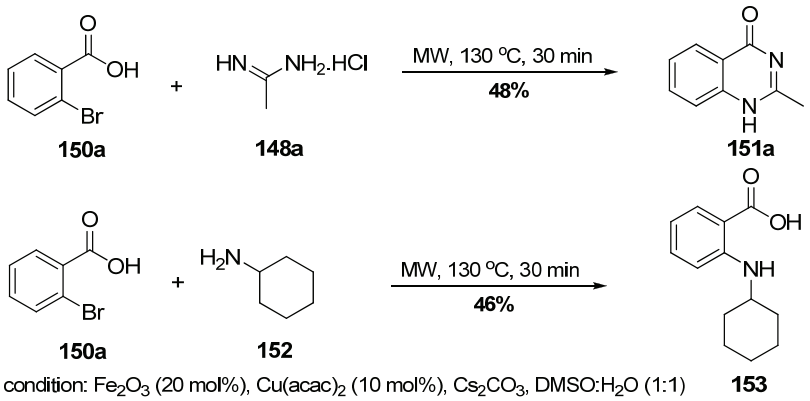
and aliphatic secondary amines afforded the desired products in good yields (70-90%). A range of substituted aryl halides were also tested with morpholine under the optimized reaction condition. Commonly, electron-rich and -poor substituted aryl halides behave similarly. However, the impact of steric 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[93] 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 $K_3PO_4 \cdot H_2O$ (2 equiv). At 125 ^oC 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 $FeCl_3 \cdot 6H_2O$/ rac-*trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine as the catalytic system.



Scheme 38. Iron-catalyzed cascade synthesis of 1,2,4-benzothiadiazine 1,1-dioxide and quinazolinone derivatives **149** and **151**.

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 ^oC 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.



Scheme 39. Iron/copper-catalyzed synthesis of 2-methylquinazolin-4(3H)-one **151a** and 2-(cyclohexylamino) benzoic acid **153** under microwave irradiation.

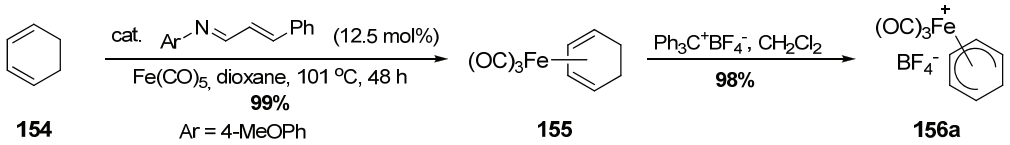
Recently, Liu *et al*. have published another attractive and environmentally benign catalytic system for iron/copper-catalyzed C-N cross coupling reactions of aryl halides with amines in the presence of water under microwave irradiation.[100] Optimum results were obtained by applying Fe_2O_3 (20 mol%), $Cu(acac)_2$ (10 mol%), Cs_2CO_3 in a mixture of DMSO and H_2O (1:1) at 150 ^oC 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*-alkylanthranilic 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(η^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(η^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]



154 **155** **156a**

Scheme 40. Synthesis of the iron-coordinated cyclohexadienylium salt **156a**.

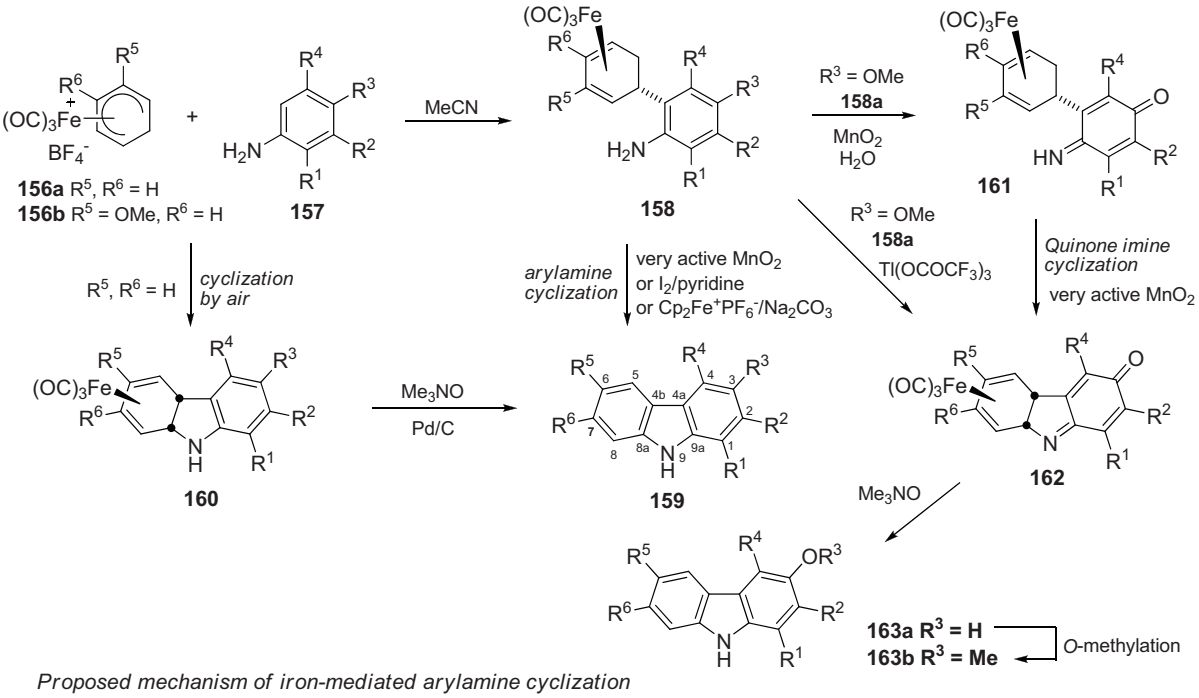
Knölker *et al*. used iron-diene complexes **156** in the synthesis of a broad range of biologically active alkaloids such as carbazoles and lycorine alkaloids (Figures 6).[104] The two key steps of the construction of the carbazole skeleton involved first, the C-C bond formation by electrophilic aromatic substitution of arylamines by complexes **156** to generate the arylamine-substituted tricarbonyl(η^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

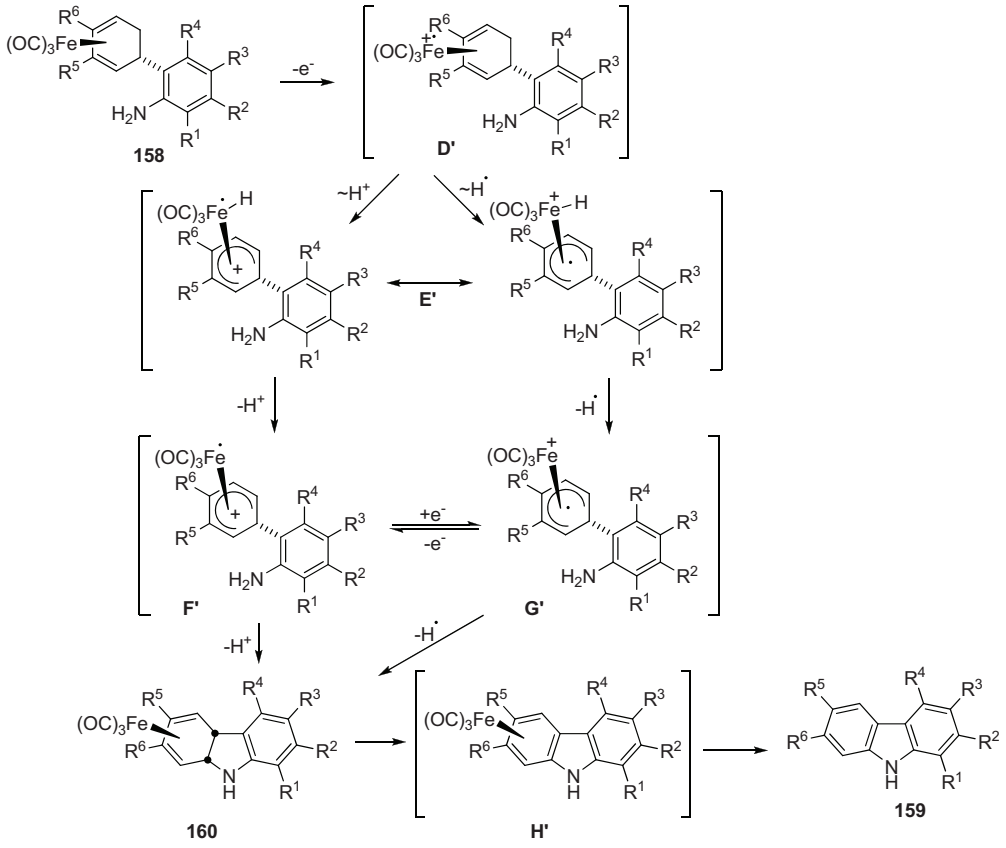
hexafluorophosphate in the presence of sodium carbonate. From deuterium labelling experiments it is known,[105] that the cyclization is initiated by single electron transfer to give a radical cation **D'** followed by *syn*-stereospecific hydrogen transfer to intermediate **E'** and subsequent dehydrogenation *via* complexes **F'** and **G'** to afford **160**. Dehydrogenation and spontaneous demetalation of dihydrocarbazole **160** provided the carbazole derivative **159** *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 *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 *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).

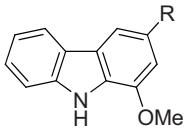


Proposed mechanism of iron-mediated arylamine cyclization

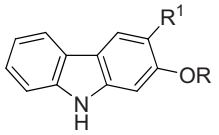


Scheme 41. Three different procedures for iron-mediated synthesis of carbazoles.

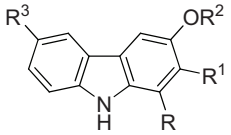
Oxygenated Tricyclic Carbazole Alkaloids



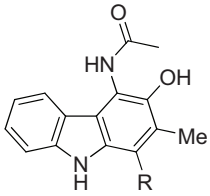
Murrayafoline A (164)[b] R = Me
Koenoline (165)[b] R = CH_2OH
Murrayanine (166)[a] R = CHO
Mukoeic acid (167)[a] R = COOH
Mukonine (168)[a] R = COOMe



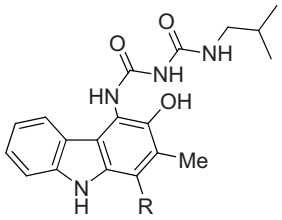
2-Methoxy-3-methyl-carbazole(169)[a]
R, R^1 = Me
Mukonidine (170)[c]
R = H, R^1 = COOMe



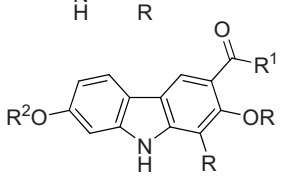
4-Deoxycarbazomyzin B (171)[a,b] R, R^1, R^2 = Me; R^3 = H
Carazostatin (172)[b] R = $(CH_2)_6Me$; R^1= Me; R^2, R^3 = H
Hyellazole (173)[a,b] R = Ph; R^1, R^2 = Me; R^3 = H
Isohyellazole (174)[a,b] R = Me; R^1 = Ph; R^2 = Me; R^3 = H
6-Chlorohyellazole (175)[a] R = Ph; R^1, R^2 = Me; R^3 =Cl



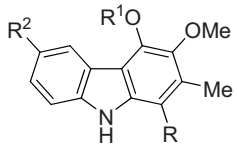
Antiostatin A_1 (176)[a] R = $(CH_2)_4Me$
Antiostatin A_2 (177)[a] R = $(CH_2)_2CH(Me)CH_2Me$
Antiostatin A_3 (178)[a] R = $(CH_2)_4CH(Me)_2$
Antiostatin A_4 (179)[a] R = $(CH_2)_6Me$



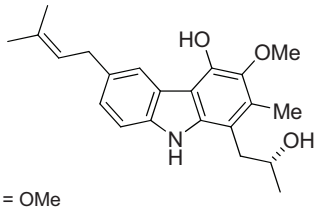
Antiostatin B_2 (180)[a]
R = $(CH_2)_5Me$
Antiostatin B_3 (181)[a]
R = $(CH_2)_4CH(Me)_2$
Antiostatin B_4 (182)[a]
R = $(CH_2)_6Me$
Antiostatin B_5 (183)[a]
R = $(CH_2)_5CH(Me)_2$



7-Metoxy-*O*-methylmukonal (184)[a]
R, R^2 = Me; R^1 = H
Clausine H (185)[a] R, R^2 = Me; R^1 = OMe
Clausine O (186)[a] R, R^1, R^2 = H
Clausine K (187)[a] R = Me; R^1 = OH; R^2 = Me

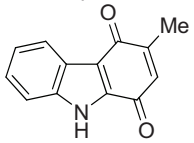


Carbazomycin A (188)[b,c] R, R^1 = Me; R^2 = H
Carbazomycin B (189)[a] R = Me; R^1, R^2 = H
Carbazomycin C (190)[a] R = Me, R^1 = H; R^2 = OMe
Carbazomycin D (191)[b] R, R^1 = Me; R^2 = OMe
Carbazomycin E (192)[a] R = CHO; R^1, R^2 = H

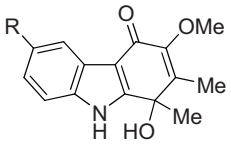


Neocarazostantin B [(*R*)-193)][c]

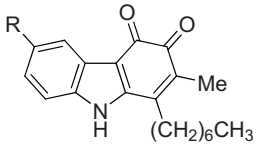
Carbazolequinone Alkaloids



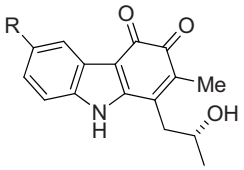
Murrayaquinone A (194)[b]



Carbazomycin G (195)[a] R = H
Carbazomycin H (196)[a] R = OMe

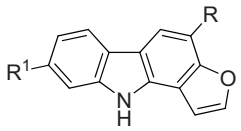


Carbazoquinocin C (197)[c]



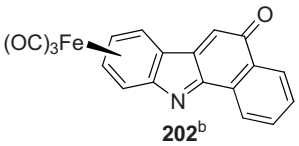
Carquinostatin A [(*R*)-198][c]
R = prenyl
Lavanduquinocin [(*R*)-199][c]
R = β-cyclolavandulyl

Furocarbazole Alkaloid



Furostifoline (200)[a]
R = Me; R^1 = H
Furoclausine A (201)[a]
R = CHO; R^1 = OH

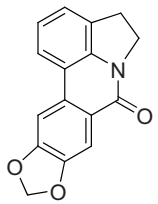
Benzoannulated Carbazole Derivative



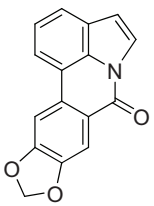
202[b]

The the iron-mediated process for oxidative cyclization
[a]arylamine cyclization
[b]quinone imine cyclization
[c]oxidative cyclization by air

Lycorine alkaloids

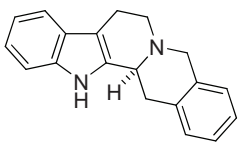


Anhydrolycorinone (203)

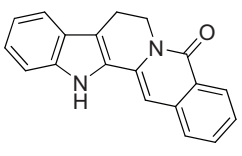


Hippadine (204)

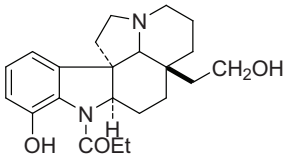
Other alkaloids



Demethoxycarbonyldihydro-gambirtannine (205)



Norketoyobyrine (206)

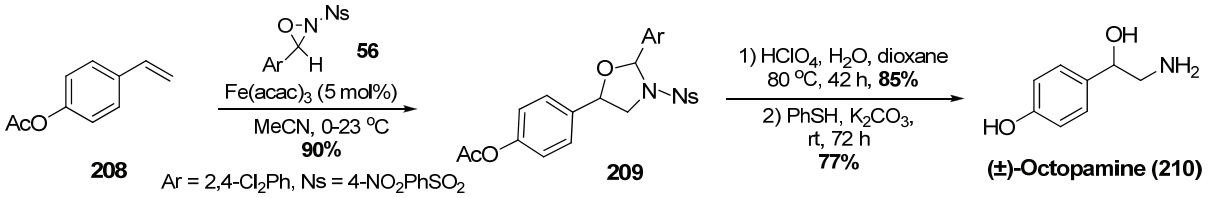


Limaspermine (207)

Figure 6. Alkaloids prepared by iron-mediated synthetic approach.

2.4.2 Iron-catalyzed synthesis of octapamine

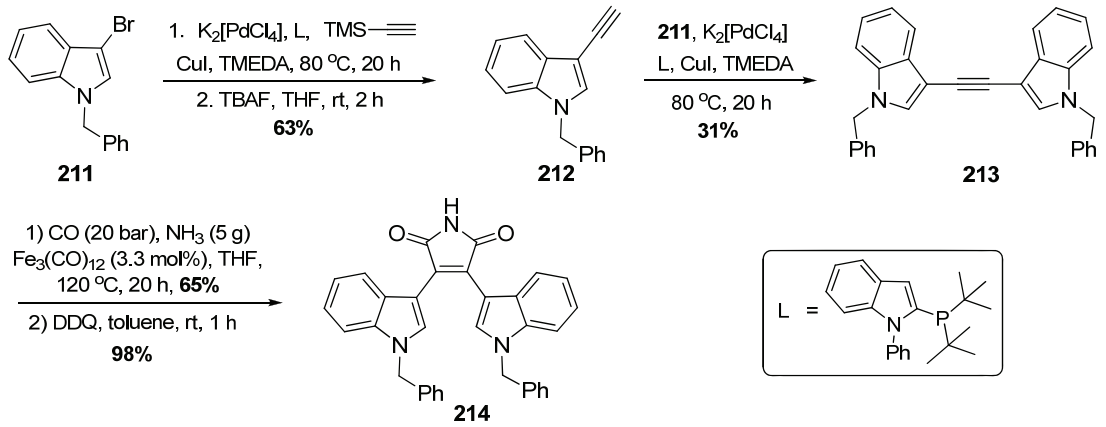
With the success of iron-catalyzed aminohydroxylations (see chapter 2.1.5), Yoon and co-worker have demonstrated the usefulness of their method in the preparation of (±)-octapamine (**210**) (Scheme 42).[31] The reaction of 4-acetoxystyrene (**208**) with oxaziridine **56** in the presence of $Fe(acac)_3$ (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**).

2.4.3 Iron-catalyzed synthesis of maleimides

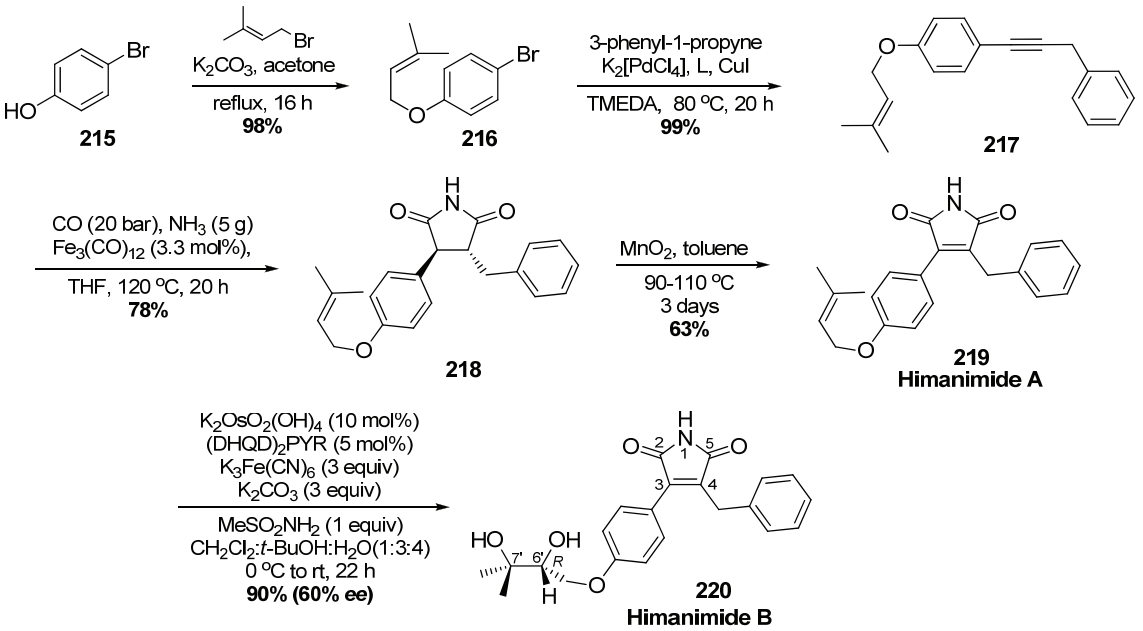
Encouraged by the successful synthesis of various maleimides using iron-catalyzed carbonylation as a key step (see chapter 2.2.6), we have applied our catalytic methodology in the synthesis of arcyriarubin derivative **214** (Scheme 43),[49a] and himanimide A and B (**219** and **220**) (Scheme 44).[106]



Scheme 43. Short synthesis of the arcyriarubin intermediate **214**.

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]



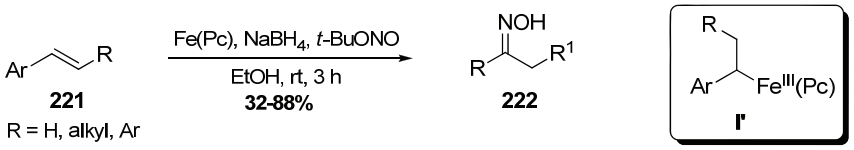
Scheme 44. Short synthesis of the himanimide A and B (**219** and **220**).

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*-

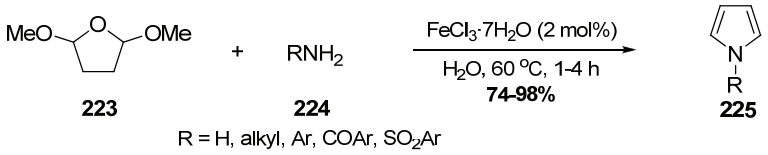
butyl nitrite. It was found that the reaction of aryl-substituted olefins **221** with *tert*-butyl nitrite and sodium borohydride in the presence of iron(II) phthalocyanine leads to the formation of oximes **222** in moderate to high yields (Scheme 45).[109] The reaction can be performed in a Schlenk tube but when the reaction was performed in autoclave with additional 10 bar H_2, the yield of the desired oxime increased significantly. The reaction was proposed to proceed *via* σ-alkyliron(III) complex **I'**. 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).[110] The reaction is catalyzed by $FeCl_3 \cdot 7H_2O$ (2 mol%) in water to obtain the heterocyclic products **225** in high to excellent yields.

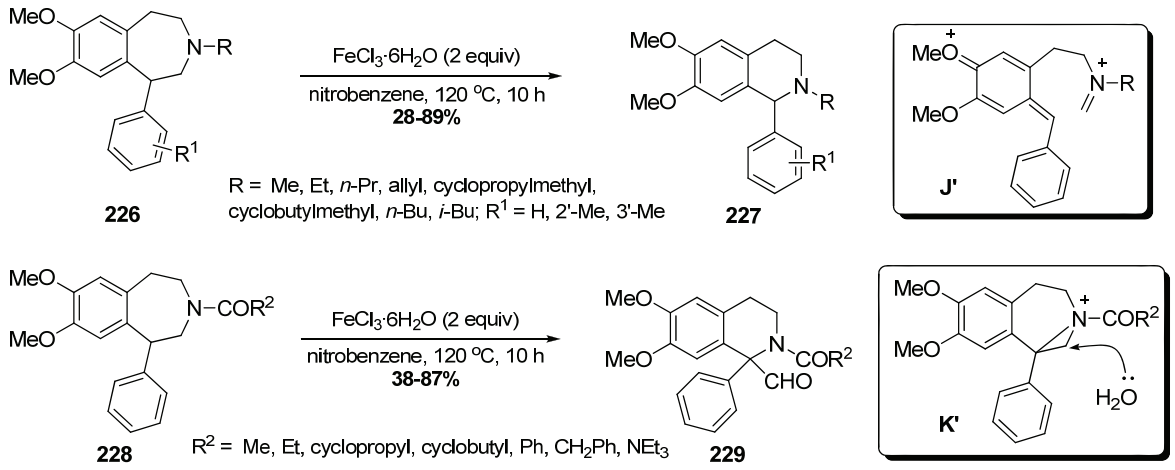


Scheme 46. Iron-catalyzed synthesis of *N*-substituted pyrroles **225**.

2.5.3 Rearrangements

Zhang and co-worker discovered that $FeCl_3 \cdot 6H_2O$ promotes skeleton rearrangements of 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines to generate tetrahydroisoquinolines in nitrobenzene (Scheme 47).[111] 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**.

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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).

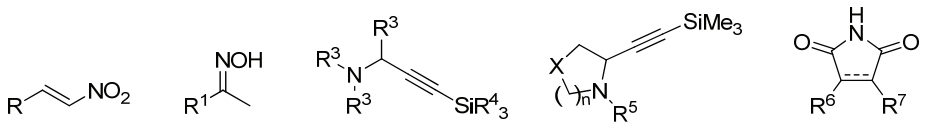


Figure 7. The synthesized nitrogen-containing compounds.

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 $NaNO_2$ 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

Irina Jovel, Saisuree Prateeptongkum, Ralf Jackstell, Nadine Vogl, Christoph Weckbecker, Matthias Beller*, *Adv. Synth. Catal.* **2008**, *350*, 2493-2497.
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

Saisuree Prateeptongkum, Irina Jovel, Ralf Jackstell, Nadine Vogl, Christoph Weckbecker, Matthias Beller*, *Chem. Commun.* **2009**, 1990-1992.
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

Irina Jovel, Saisuree Prateeptongkum, Ralf Jackstell, Nadine Vogl, Christoph Weckbecker, Matthias Beller*, *Chem. Commun.* **2010**, *46*, 1956-1958.
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

Saisuree Prateeptongkum, Katrin Marie Driller, Ralf Jackstell, Anke Spannenberg, Matthias Beller*, *Chem. Eur. J.* **2010**, *16*, 9606-9615.
DOI: 10.1002/chem.201000369

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

Saisuree Prateeptongkum, Katrin Marie Driller, Ralf Jackstell, Matthias Beller*, *Chem. Asian. J.* **2010**, *5*, 2173-2176.
DOI: 10.1002/asia.201000384

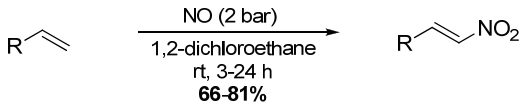
Contributions

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.

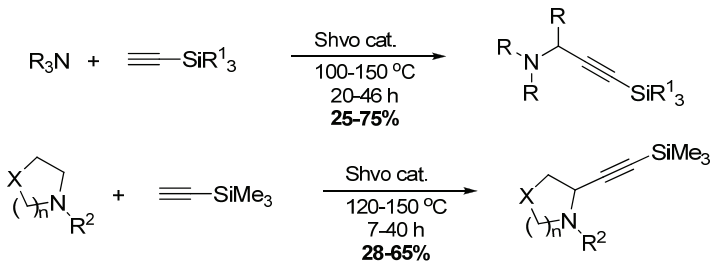
In order to use nitric oxide (NO) as the nitrogen source in nitration reaction, the reaction of NO with olefins has been investigated. The direct nitration of a range of olefins underwent successfully at room temperature leading to the formation of nitroolefins in high regioselectivity and good yields 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.

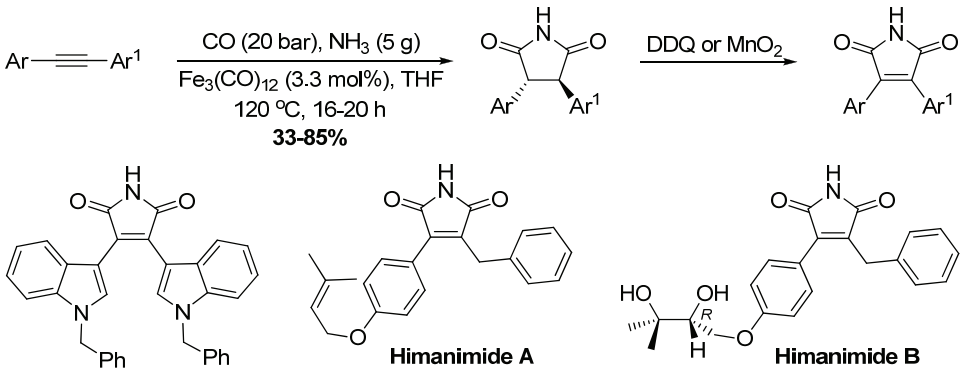
tert-Butyl nitrite, which was known as efficient NO equivalent, can also be used for the synthesis of oximes from styrenes by using a biomimetic iron phthalocyanine complex catalyst and readily available reductant ($NaBH_4$). For details, see Publication 4.2, *Chem. Commun.* **2009**, 1990-1992.

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.



Scheme 49. The synthesis of propargyl amines.

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, himanimideA 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.



Scheme 50. The synthesis of succinimides and maleimides.

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

Saisuree Prateeptongkum