Iron(III) as Lewis Acid Catalyst in Organosilicon and Carbonyl Chemistry

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Remember kids,
the only difference between
screwing around and science,
is writing it down.

Adam Savage

PREFACE

The present work was carried out at the Laboratory of Organic Chemistry, Department of Natural Sciences, Åbo Akademi University between the years 2009 and 2015. Financial support from the former National Graduate School of Organic Chemistry and Chemical Biology, Stiftelsen för Åbo Akademi, Magnus Ehrnrooth foundation, Orion Farmos Research foundation, Rector of Åbo Akademi and Kemian Päivien säätiö is gratefully acknowledged.

I wish to express my gratitude to my supervisor Professor Reko Leino for giving me the opportunity to join the research group, giving me a chance to venture into the world of iron catalysis and for his patience and support during these years. Also, I wish to thank Professor Per-Ola Norrby for my short visit to the University of Gothenburg, and for guiding me on my short venture into the world of computational chemistry and molecular modelling.

I am very thankful to Professor Timo Repo and Professor Hans Adolfsson for reviewing my thesis. Furthermore I wish to thank Dr. George Britovsek for accepting to be my opponent.

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Many thanks to people who have participated in my hobbies outside the laboratory, with special mention to Jani Viuhkola, Ville Kiviharju and Joonas Eskelinen for many bruises and muscle aches, Timo Valta for some interesting moments in the kitchen and the families of Palo and Juntunen. I also wish to thank Rami Nylund, Asko Kuuskosi and Marko Koskinen for a number of fun evenings. I wish to thank Erkki Honkanen for teaching me how to work with iron in more traditional way and his wife for great hospitality.

Finally my sincerest gratitude goes to my wife, family and relatives, for encouragement and support on my endeavours wherever they may have led me.

Åbo, April 2015

ABSTRACT

Iron is one of the most common elements in the earth's crust and thus its availability and economic viability far exceed that of metals commonly used in catalysis. Also the toxicity of iron is miniscule, compared to the likes of platinum and nickel, making it very desirable as a catalyst. Despite this, prior to the 21st century, the applicability of iron in catalysis was not thoroughly investigated, as it was considered to be inefficient and unselective in desired transformations. In this doctoral thesis, the application of iron catalysis in combination with organosilicon reagents for transformations of carbonyl compounds has been investigated together with insights into iron catalyzed chlorination of silanes and silanols.

In the first part of the thesis, the synthetic application of iron(III)-catalyzed chlorination of silanes (Si-H) and the monochlorination of silanes (SiH_2) using acetyl chloride as the chlorine source is described. The reactions proceed under ambient conditions, although some compounds need to be protected from excess moisture. In addition, the mechanism and kinetics of the chlorination reaction are briefly adressed.

In the second part of this thesis a versatile methodology for transformation of carbonyl compounds into three different compound classes by changing the conditions and amounts of reagents is discussed. One pot reductive benzylation, reductive halogenation and reductive etherification of ketones and aldehydes using silanes as the reducing agent, halide source or cocatalyst, were investigated. Also the reaction kinetics and mechanism of the reductive halogenation of acetophenone are briefly discussed.

SAMMANFATTNING

Järn är en av de vanligaste grundämnena i jordskorpan. Den goda tillgänglighet gör att den ekonomiska lönsamheten för användningen av järn som katalysator vida överstiger den för övriga metaller. Järn är heller inte giftigast i jämförelse till många andra metaller som används som katalysatorer, liksom platina och nickel. Trots detta har andvändningen av järn som katalysator inte undersökts fullständigt, eftersom det har ansetts vara ineffektivt och oselektivt i de önskade kemiska transformationerna. I denna avhandling har tillämpningen av järn som katalysator i reaktioner mellan kiselorganiska reagens och karbonylföreningar undersökts. Därtill har studier kring klorering av silaner och silanoler med järn som katalysator undersökts.

I den första delen av avhandlingen, beskrivs den syntetiska tillämpningen av järn (III)-katalyserad klorering av silaner (Si-H) och monoklorering av silaner (SiH_2) med acetylklorid som klorkälla. Dessa reaktioner fortskrider under milda förhållanden, även om vissa föreningar behöver skyddas från fukt. Dessutom behandlas kort mekanismen och kinetiken för kloreringsreaktionen.

Den andra delen av denna avhandling diskuterar av en mångsidig metod för syntes av tre olika substansklasser från karbonylföreningar. En reduktiv bensylering i ett reaktionskärl, reduktiv halogenering och reduktiv etersyntes av ketoner och aldehyder med silaner som reduktionsmedel och en halidkälla eller kokatalysator, undersöktes. Också, kinetiken och mekanismen för den reduktiva halogeneringen av acetofenon diskuteras kort.

LIST OF ORIGINAL PUBLICATIONS AND MANUSCRIPTS

I Savela, R.; Zawartka, W.; Leino, R. **Iron-Catalyzed Chlorination of Silanes,** *Organometallics*, **2012**, *31*, 3199-3206.

II Savela, R.; Grénman, H.; Sundelin, H.; Norrby, P.-O.; Murzin, D.; Leino, R. **Kinetic and Theoretic Investigation of Iron(III) Catalyzed Silane Chlorination,** manuscript in review.

III Savela, R.; Majewski, M.; Leino, R. **Iron-Catalyzed Arylation of Aromatic Ketones and Aldehydes Mediated by Organosilanes,** *Eur. J. Org. Chem.* **2014**, 4137-4147.

IV Savela R.; Wärnå, J; Murzin, D.; Leino R. **Iron Catalyzed Halogenation of Benzylic Aldehydes and Ketones,** *Catal. Sci. Technol.* **2015***, 5,* 2406-2417.

V Savela, R.; Leino, R. **Synthesis of Ethers from Carbonyl Compounds by Iron(III) and Silyl Chloride Catalyzed Reductive Etherification**, *Synthesis,* in Press. **DOI:** 10.1055/s-0034-1380155.

CONTRIBUTION OF THE AUTHOR

This thesis is based on 4 publications and 1 manuscript. The author of this thesis is the main author of all papers. The author is fully responsible for the experimental work presented in this thesis from publications **I** and **III**-**V**. The experimental work in manuscript **II** was carried out together with Heidi Sundelin. The author is also responsible for the computational investigation under the supervision of Professor Per-Ola Norrby on reaction mechanism and transition states (Manuscript **II**) presented in Chapter 2.4. The kinetic modeling presented in Chapters 2.4 and 3.3.3. was performed in collaboration with Dr. Henrik Grénman, Professor Johan Wärnå and Professor Dmitry Yu. Murzin at the Laboratory of Industrial Chemistry and Reaction Engineering at Åbo Akademi University.

LIST OF ABBREVIATIONS

EtOAc	Ethylacetate
MeOAc	Methylacetate
DCM	Dichloromethane
DCE	1,2-dichloroethane
THF	Tetrahydrofuran
DEE	Diethyl ether
ACN	Acetonitrile
OAc	Acetate
OTf	Triflate
Me	Methyl
Et	Ethyl
Ph	Phenyl
t-bu	t*ert*-Butyl
i-Pr	*iso*-Propyl
Np	Naphthyl
acac	Acetylacetonate
eq	Equivalent
r.t.	Room temperature
NMR	Nuclear magnetic resonance
GC	Gas chromatography
fid	Flame ionization detector
MS	Mass spectrometer
DFT	Density functional theory

CONTENTS

1. INTRODUCTION

1.1. Aim of This Thesis

In the work discussed in this thesis, new and modified iron(III)-catalyzed methodologies using silanes as cocatalyst or reagents for production of fine chemicals as well as pharmaceutical intermediates were investigated. The aim was to discover iron-catalyzed reactions that could be operated under benign and economically viable conditions, using solvents such as ethyl acetate or hexane and operating at ambient pressure and temperature. Furthermore, the reactions were planned to be as user friendly as possible with simple work-up and purification procedures. The possible scale-up of the reactions developed was also briefly investigated.

1.2. Organosilicon Chemistry

While the silicates in clay have been used in pottery for centuries, the element silicon was first purified and characterized by Jöns Berzelius in 1823, published in 1824, by reduction of potassium fluorosilicate with potassium.[1] Today silicon is most commonly prepared in electric arc furnaces from silicon dioxide.[2] Both methods are illustrated in Scheme 1.1. Shortly after Berzelius had reported the formation of silicon, he also reported the formation of silicon tetrachloride ($SiCl_4$)

from the reaction of silicon with chlorine gas, followed by Wöhler's isolation of silane (SiH_4) and trichlorosilane ($SiHCl_3$) in 1857.[3] In 1863, the first example of an orgnosilicon compound possessing an actual Si-C bond was brought into the daylight by Charles Friedel and James Crafts.[4] By reacting silicon tetrachloride with diethylzinc they managed to synthesise tetraethylsilane [$(C_2H_5)_4Si$], thereby giving birth to the field of oganosilicon chemistry.

$$K_2SiF_6 + 4\,K \longrightarrow Si + 6\,KF$$

Method used by Berzelius in 1823

$$SiO_2 + 2\,C \longrightarrow Si + 2\,CO$$

Method used today

Scheme 1.1. Preparation of elemental silicon

Undoubtedly polymeric siloxanes, often called silicones, are one of the most important applications in the field of organosilicon chemistry, being widely used in the everyday life both in industry and laboratory, in household goods and medicine.[5,6] Organosilanes are used also by organic chemists, often as reducing agents,[7] in derivatisation of organic molecules as protecting groups,[8] or for steric bulk in amino-functionalized catalysts.[9] Organosilanes also find use as Lewis acids in catalysis,[10] and for transfer of substituents, such as allyl, from silyl compounds to organic molecules.[11] In medicinal chemistry, new applications are emerging due to the ongoing search for new drug candidates where carbon centers have been replaced by silicon atoms.[12] Overall, organosilanes play an important role in several partially overlapping fields ranging from organic, organometallic and medicinal chemistry to polymer science, and have proven as versatile materials for the synthesis of several important catalysts, reactants and reagents in synthetic chemistry.[5,13]

1.3. Catalysis

Catalysis is for chemists one of the most efficient methodologies for production of various compounds and building blocks, indispensable for pharmaceuticals, agrochemicals, flavors, fragrances and advanced materials. Catalysis is an extremely broad field of applied chemistry and therefore the number of different catalysts used in various applications is vast. Catalysts range from proton (H^+), one of the most common catalysts in chemical reactions, to solid acids and bases, transition metals, transition metal complexes and salts, organocatalysts and enzymes. The power of catalysis has been acknowledged four times by the Nobel prize in Chemistry during the first decade of the 21st century:[14]

2001: Williams S. Knowles and Ryoji Noyori for chirally catalyzed hydrogenation reactions and K. Barry Sharpless for chirally catalyzed oxidation reactions.

2005: Yves Chauvin, Robert H. Grubbs and Richard R. Schrock for the development of metathesis method in organic syhtesis.

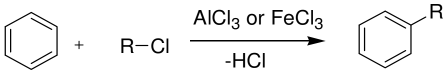
2007: Ertl Gerhard for his studies of chemical processes on solid surfaces.

2010: Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for palladium-catalyzed cross couplings in organic synthesis.

The main function of a catalyst is to increase the rate of a reaction by lowering the energy barrier required for the transition state, thus leading to shorter reaction times and lower operating temperatures. Ideally, catalysts differ from other reactants in chemical reactions by not being consumed during the course of the reaction. While in best cases catalyzed reactions can be carried out at room temperature under atmospheric conditions, it is quite common that at least the exclusion of moisture and air is required using nitrogen or argon as the gas atmosphere. While the basic methodology of catalysis is rather simple, the application and exact mechanism of action can be extremely complex. For example, a catalyst may favourably influence the rate of the reaction by polarizing chemical bonds via binding to substrate or by forming new intermediates between the catalyst and the substrate.

In general, catalysis can be divided into two modes of operation: Homogeneous and heterogeneous catalysis, both presenting a differing array of pros and cons. Using solid acids or bases or by supporting the catalyst on solid carrier making the catalyst by definition insoluble in the reaction mixture, the catalyst can be more easily separated from the reaction medium. In heterogeneous catalysis, the power lies in the ease of purification and possibility for constant-flow yielding smaller amount of waste and fewer separation procedures making it the preferred method for industrial applications. In contrast to heterogeneous catalysis, a homogeneous catalyst is fully dissolved in the reaction mixture, often yielding a higher degree of selectivity and reactivity. The downside is that the catalyst has to be separated from the product, making the recycling of the soluble catalyst difficult, which in turn leads to economical losses in cases of expensive transition metals. Yet, homogeneous catalysis is often the main interest of the organic chemists, due to often simpler customization of the catalyst and the possibility for more detailed examination of the reaction mechanism by spectroscopic means.

1.4. Friedel-Crafts Reaction

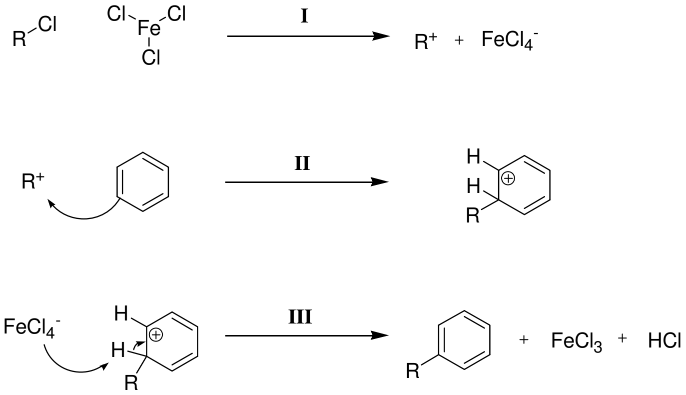


Scheme 1.2. Friedel-Crafts Reaction

One of the oldest, well known and most utilized iron catalyzed methods in organic chemistry are the Friedel-Crafts alkylation and acylation developed by Charles Friedel and James Crafts in 1877,[15] illustrated in Scheme 1.2. This was also the first example of a Lewis acid catalyzed reaction in the history of Organic Chemistry. While originally aluminium chloride was used as the catalyst, a number of other catalysts have been investigated during the past 100 years for this reaction including transition metal salts,[16] organocatalysts,[17] carbon monoxide,[18] solid catalysts such as zeolites and clays,[19] and superacids.[20] In recent years enantioselective methods have also been under investigation to further extend the application areas of the Friedel-Crafts reaction.[21] The main sources of the electrophiles are typically alkyl or acyl halides but a variety of other types of reagents can also be employed.[22]

Friedel-Crafts reaction is of significant importance for both laboratory synthesis and industrial applications. Notably, Friedel-Crafts alkylation is one of the fundamental catalytic methods used for producing a multitude of organic compounds which, in turn, are useful intermediates for dyes, pharmaceuticals and cosmetics, among others.[22]

1.4.1. Mechanism of the Friedel-Crafts Reaction



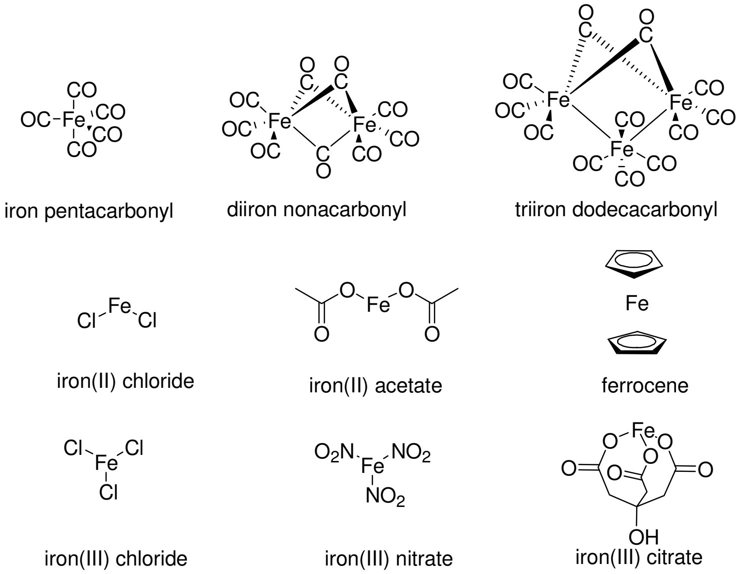
Scheme 1.3. Mechanism of Friedel-Crafts Reaction

Both Friedel-Crafts alkylation and acylation proceed by the general pathway of electrophilic aromatic substitution with the catalyst activating the electrophile, which can either be an alkyl or acyl halide. A general mechanism[22e,23] is illustrated in Scheme 1.3 in three steps. First (**I**) the catalyst abstracts halogen from the electrophile producing a carbocation which then can be attacked by the electrons from the aromatic benzene ring (**II**). The aromaticity is recovered with abstraction of proton from the intermediate with chloride ion releasing hydrochloric acid as byproduct and regenerating the catalyst (**III**). Generally this type of reaction mechanism is accepted and used in advanced level organic chemistry textbooks for undergraduates, but computational studies have also implicated C-H activation as a possible mechanistic pathway for few selected catalysts.[24]

In the case of alkyl halides as electrophiles, the downside is that the gained product is more nucleophilic than the starting material which can lead to multiple alkylations. Also if the carbocation formed is not tertiary, rearrangement of the alkyl carbocation can take place leading into mixtures. The product composition usually follows the relative stabilities of the respective carbocations, secondary favoured over primary. While this can be avoided by using acyl halides as the electrophiles, a subsequent reduction of the formed ketone is required. Chelation of the catalyst to formed product can also take place, especially with aluminium and iron Lewis acid catalysts. This can lead to deactivation of the catalyst, which forces use of the equivalent amount of “catalyst“ in order for the reaction to proceed.

1.5. Iron in Catalysis

Transition metal catalyzed methods for organic synthesis often use expensive and/or toxic transition metals such as platinum, palladium, gold, nickel and mercury which has led to significant concern about possible metal residues in the final product and waste, especially in pharmaceuticals and food additives.[25] This, in turn, will increase the expenses in process and waste management in order to guarantee product safety and to minimize the environmental impact of the produced waste. On the one hand, the use of iron as catalyst would enable cheaper and safer methodologies, but on the other hand, it often suffers from poor reactivity or selectivity in comparison to the more "noble" metals. Partly due to these reasons, iron has only recently received growing interest in the field of catalysis.[26] On industrial multi-ton scale, iron has only been used as a catalyst in the Haber-Bosch process for synthesis of ammonia from the beginning of the 20th century, as well as in Fischer-Tropsch process.



iron pentacarbonyl diiron nonacarbonyl triiron dodecacarbonyl

iron(II) chloride iron(II) acetate ferrocene

iron(III) chloride iron(III) nitrate iron(III) citrate

Figure 1.1. Examples of readily available iron compounds and salts

Organoiron chemistry first attained interest in 1891 by the discovery of pentacarbonyl iron,[27] later followed by ferrocene in 1951.[28] The Reppe synthesis also brought iron catalysis into the limelight,[29] as well as iron catalyzed cross-coupling reactions of Grignard reagents with organic halides.[30] The use of other iron compounds predate these discoveries, such as ferrocyanides, from which the most well know is Prussian blue, a well-known dye with a wide variety of applications. Selected commonly employed organoiron compounds and salts are illustrated in

Figure 1.1. In addition to these, iron sulphates and phosphates are also widely used in a multitude of applications ranging from academia to everyday life.

One of the earliest investigations on iron catalyzed reactions was the use of iron carbonyls as catalyst for hydrogenation of olefins.[31] For general applicability the downside is the high pressure (250-300 atm) and high temperature (~200 °C) required. The methodology was further modified to involve photocatalysis, enabling much milder conditions and extension from hydrogenation to isomerization reactions as well as to hydrosilylation.[32] The mechanism of this iron carbonyl catalyzed hydrogenation has also been investigated widely both by experimental and computational means.[33] Concomitantly, iron catalyzed transfer hydrogenation reactions were developed by Noyori, Vancheesan and Bianchini.[34]

Iron catalyzed coupling reactions emerged in the early 1940s,[35] but in the following years only a few iron catalyzed reactions were published, with focus on iron catalyzed Grignard reactions.[36] In the late 20th century, renewed interest in iron catalyzed reactions emerged[26] including iron catalyzed olefin polymerization reactions.[37] Yet it is only recently, that iron catalyzed reactions have enjoyed a true renaissance.

1.5.1. Recent Advances

The past fifteen years have seen an immense increase in iron catalyzed reactions in many areas of organic chemistry,[38] and more recently chiral iron catalysts have been used for asymmetric synthesis.[39] Iron catalyzed reduction reactions[40] have also received significant interest, especially hydrogenation reactions have been investigated in detail. Transfer hydrogenation has proven to be a convenient methodology for synthesis of alcohols from ketones and aldehydes using various transition metal catalysts. In recent years, investigations into iron catalyzed transfer hydrogenation have sparked significant interest with the methods developed being extended to a large number of substrates.[41] Furthermore, the reaction mechanisms of iron catalyzed transfer hydrogenations have been under intense experimental and computational investigation by Morris and coworkers.[42] The most recent advances in iron catalyzed hydrogenation and transfer hydrogenation are collected in Table 1.1.

Table 1.1. Iron catalyzed reduction reactions.

Hydrogenation	Transfer Hydrogenation	Borohydrides and hydrazines	Hydrometallation	Hydrosilylation
Alkenes and Alkynes[43]	Ketones and Aldehydes[44]	Reductive amination[45]	Hydroboration[46]	Amides, imines and cyano[47]
Imines to amines[48]	Asymmetric[49]	Reduction of olefins[50,51]	Hydromagnesiation[52]	Sulfoxides to sulphides[53]
NO_2 to NH_2[54]	Imines[55]	NO_2 to NH_2[51,56]		Acid chlorides and esters to aldehydes[57]
Esters to alchols[58]	Nitroarenes[59]	Dehydroxylation[60]		Acid chlorides and esters to alcohols[61]
Carbonyl[62]	Alkenes and Alkynes[63]	Reductive cyclization[64]		Reductive amination[65]
Reductive amination[66]				Allylation[67]

To a lesser extent, iron has been used as a catalyst for reactions using borohydrides and hydrazines as reducing agents. A number of iron catalyzed hydrometallation reactions, including hydrosilylation, hydroboration and hydromagnesiation have also gained interest in the last decade. Hydrosilylation is one of the most studied fields of iron catalyzed hydrometallation reactions and is discussed in more detail in Chapters 1.5.2 and 1.5.3.[68] The most recent advances in iron catalyzed reduction reactions are collected in Table 1.1.

Table 1.2. Iron catalyzed coupling reactions

Grignard	Organometallic reagents	Oxidative	Name reactions
sp^2-sp^3[69]	Organocuprates[70]	C-C[71]	Mizoroki-Heck[72]
sp^2-sp^2[73]	Organozinc[74]	C-O[75]	Negishi[76]
sp-sp^3[77]	Organoalunimium[78]	C-S[79]	Sonogashira[80]
sp-sp^2[81]		C-N[82]	Copper free Sonogashira[83]
sp^3-sp^3[84]		Heterocycle synthesis[85]	High pressure Suzuki Miyaura[86]
Carboxylic acid synthesis[87]			Ambient pressure Suzuki Miyaura[88]

In iron catalyzed coupling reactions,[89,90] a strong focus has been on Grignard reagents but also other organometallic reagents have found uses in this field. By far the most diverse field has been oxidative coupling reactions using peroxides or oxygen as the oxidant.[91] The use of iron as catalyst has also been extended to Mizoroki-Heck type reactions and Negishi reaction. Iron catalyzed Sonogashira reactions have also been investigated but often a copper salt is needed as cocatalyst for the reaction to proceed.[92] The first step towards iron catalyzed Suzuki-Miyaura reaction was performed under high pressure, after which ambient pressure Suzuki-Miyaura type coupling reactions have emerged mainly by laboratories of Bedford and Nakamura.[88] The most recent advances in iron catalyzed coupling reactions are collected in Table 1.2.

Table 1.3. Recent advances in varied fields of iron catalyzed reactions.

Cyclization[93]	Cascade[94]	Oxidation[95]	Amination[96]	Alkyne carbonyl metathesis[97]
Cycloadditions[98]	Domino[99]	Epoxidation[100]	Hydroaminaton[101]	H-Si and R-CN metathesis[102]
Cycloisomerization[103]	Kinetic resolution[104]		C-H amination[105]	Polymerization[106]
	C-H activation[107]		Haloamination[108]	
			Aromatic amination[109]	

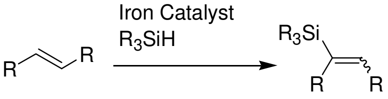
Already prior to the 21th century iron catalyzed cycloaddition reactions[26] were a common field of study. Yet new investigations in this field keep emerging. The use of iron as catalyst for cascade and domino reactions, as well as for kinetic resolution and C-H activation has gained attention in recent years. Similarly to iron catalyzed oxidative coupling reactions, the use of iron as catalysts for oxidation and epoxidation reactions has been described in various reports for a number of applications. Alongside oxidation reactions a significant field of study has been iron catalyzed amination reactions with significant contributions to hydroamination and C-H amination. Iron catalyzed metathesis reactions have also started to emerge. Furthermore, the use of iron catalysts for polymerization reactions has reemerged.[110]

The most recent advances from these fields of iron catalyzed reactions are collected in Table 1.3.

1.5.2. Iron Catalyzed Hydrosilylation of Alkenes and Alkynes

Scheme 1.4. Iron catalyzed hydrosilylation.

Traditionally, hydrosilylations of olefins to alkenes or alkynes, illustrated for iron in Scheme 1.4, are achieved by use of platinum compounds such as chloroplatinic acid (H_2PtCl_6) or with Karsedt's catalyst, both of which are also favored by the industry. While platinum and palladium are probably the most utilized transition metals in hydrosilylation reactions, a multitude of other catalysts and methods can be used. These include other transition metals, Lewis acids, radical initiators and photocatalysis. Platinum(0) catalyzed reactions proceed via Chalk-Harrod mechanism which assumes an oxidative addition of Si-H to the metal center, followed by olefin insertion to the metal-hydride bond. The cycle is then completed by Si-C reductive elimination. The products tend to follow anti-Markovnikov addition.[111]



Scheme 1.5. Dehydrogenative silylation

The first investigation on hydrosilylation of olefins with $Fe(CO)_5$ or colloidal iron as the catalyst was published in 1962 producing variable mixtures of products from hydrosilylation (Scheme 1.4) and dehydrogenative silylation (Scheme 1.5).[112] This was followed by photocatalyzed reaction using $Fe(CO)_5$ in 1977 leading also to mixtures of products.[113] In 1993 the $Fe_3(CO)_{12}$ catalyzed reaction of styrenes with triethylsilane solely provided dehydrogenation products.[114] In 2004 Chirik and coworkers reported the Fe(0) complex illustrated in Figure 1.2, being both efficient and capable of high selectivity towards hydrosilylation of 1-hexene under ambient conditions.[115]

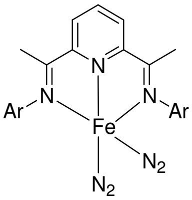
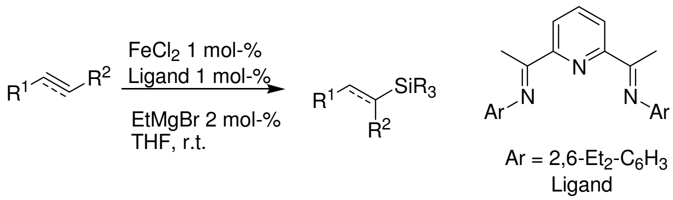


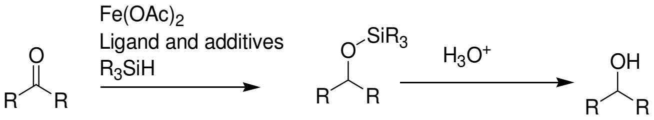
Figure 1.2. Catalyst used for hydrosilylation of 1-hexene by Chirik and coworkers.[115]

Enthaler et al. have reported the $Fe_2(CO)_9$ catalyzed hydrosilylation of alkynes to (Z)-alkenes with good selectivity.[116] The reaction was shown to be efficient in reducing diaryl-, aryl-alkyl- and ester substituted alkynes. In 2014, Thomas and coworkers published the first fully chemo-, regio- and stereoselective hydrosilylations of alkanes and alkynes using $FeCl_2$ as the precatalyst with similar ligand as used by Chirik and coworkers, illustrated in Scheme 1.6.[117]



Scheme 1.6. Chemo-, regio- and stereoselective hydrosilylation published by Thomas and coworkers. [117]

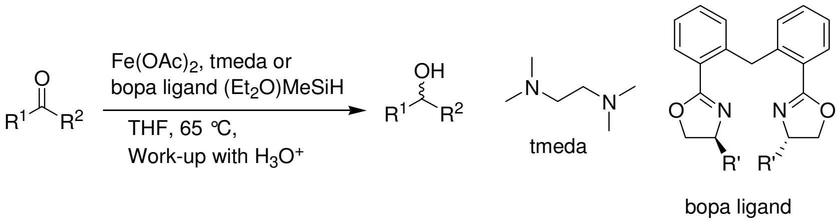
1.5.3. Iron Catalyzed Hydrosilylation of Aldehydes and Ketones



Scheme 1.7. General method of hydrosilylation followed by acid or base treatment for alcohol production.

In contrast to other reduction methods, such as hydrogenation or reduction with lithium or boron hydrides, iron catalyzed hydrosilylations of ketones and aldehydes provide a mild route to alcohols which in turn can be useful intermediates for several synthetic applications. The general methodology for iron catalyzed hydrosilylation of ketones and aldehydes following cleavage of Si-O bond by acid treatment is illustrated in Scheme 1.7. The exact reaction mechanism of iron catalyzed hydrosilylation is yet to be fully elucidated but indications from theoretical studies on iron(II) hydride complexes show that, in contrast to previously mentioned Chalk-Harrod mechanism, precoordination of the carbonyl oxygen to metal center is the preferred pathway.[118]

In the early 1990s Brunner et al. described the use of Fe(Cp)(CO) complexes for the hydrosilylation of acetophenone.[119] This was followed by Nishiyama et al. with the use of $Fe(OAc)_2$ as the precatalyst in combination with nitrogen bearing ligands for hydrosilylation of ketones, with extension to asymmetric hydrosilylation using bopa ligands with ee's ranging from 37 % to 79 %[120] illustrated in Scheme 1.8. Later, the methodology was also extended to thiophenecarboxylate ligands instead of nitrogen ligands[121] and the asymmetric hydrosilylation was further improved.[122] The methodology was extended to aldehydes by Beller and coworkers using electron rich phosphorous ligand.[123]



Scheme 1.8. $Fe(OAc)_2$ catalyzed hydrosilylation of ketones by Nishiyama et. al.

In the last few years iron catalyzed hydrosilylations of ketones and aldehydes have sparked considerable interest. The major focus has been on modification of the catalyst complexes and ligands for broadening of the substrate scope and lowering of the catalyst loading,[124] as well as for increasing the chemo- and stereoselectivity.[125] Well-defined carbene iron complexes have also been prepared and investigated for hydrosilylations of ketones and aldehydes.[126] Iron-photocatalytic switchable hydrosilylations of carboxylic acids to either alcohols or aldehydes[127] and iron catalyzed hydrosilylations of CO_2[128] have also been described.

1.5.4. General Concers Over Iron Catalysis

While iron indeed is highly promising and as a desirable catalyst, severe concerns over whether the catalytic activity actually originates from the iron species or from other metal contaminants or residues, such as palladium, have been expressed in many reports. Especially in case of $FeCl_3$, it has been shown that the catalytic activity can highly depend on the purity and source of the metal salt.[129] Copper impurities in iron salts in particular tend to be common and shown to be one of the major culprits.[129b,c] While the purity of the catalyst can be of major concern, also the trace impurities from solvents or other reagents have also been shown to be the perpetrator especially in case of palladium.[130] This has led to a tight scrutiny of iron catalyzed reactions making verification of results with high purity catalyst (for example 99.99% purity iron) a commonplace practice

1.6. References

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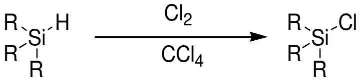
2. IRON CATALYZED CHLORINATION OF SILANES[I, II]

In this chapter the iron(III)-catalyzed chlorination and monochlorination of silanes (SiH or SiH_2) to chlorosilanes (SiCl or SiHCl respectively) is discussed. A variety of substituents were investigated as well as the use of alkoxy silanes (SiOR) and silanols (SiOH) as substrates. The reactions could also be scaled up to 95 mmol. Kinetics and mechanism of the reaction were further elaborated by kinetic and molecular modeling.

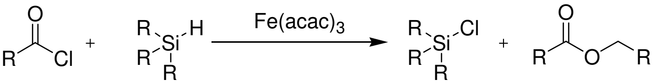
2.1. Introduction

Already in the 1950s a number of studies on the halogenation of silanes were reported.[1] In 1964, Sommer and coworkers described the widely applied procedure for chlorination of silanes (Si-H) to chlorosilanes (Si-Cl) by use of chlorine gas in tetrachloromethane, illustrated in Scheme 2.1.[2] In later work in the chlorination of silanes, heterogeneous catalysts containing Pd on alumina or carbon support have been employed with concomitant bubbling of gaseous hydrochloric acid to the reaction mixture.[3] While both of these methods allow the chlorination of chiral *stereogenic-at-silicon* silanes with retention of the stereochemistry, in order for the reactions to proceed toxic solvents are required. A radical induced halogenation of silanes in tetrachloromethane has likewise been described providing good yields of the corresponding chlorosilanes.[4]



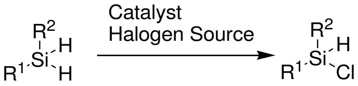
Scheme 2.1. Chlorination of silanes with chlorine gas in tetrachloromethane.

Voronkov et al. have reported the formation of chlorosilanes as a byproduct in the iron(III) acetylacetonate catalyzed reduction of carboxylic acid chlorides and aldehydes to esters, illustrated in Scheme 2.2.[5] Halogenated silanes have also been prepared using Ni(II) chloride and Pd(II) chloride catalysts in combination with suitable halogen containing reagents or solvents including tetrachloromethane.[6] Recently, the palladium dichloride based methodology has been extended for activation of Si-H bonds in THF using hexachloroethane as the halogen donor in order to avoid the use of more toxic reagents and solvents.[7]



Scheme 2.2. Reductive etherification reported by Voronkov and coworkers.[5]

A variety of chlorinating agents and methods have been published earlier for chlorination of methoxysilanes, including reactive chlorides such as acyl chlorides,[8, 9] thionyl chloride,[9, 10] phosphorous trichloride,[9, 11] phosphorous pentachloride,[12] and oxalyl chloride with aluminium trichloride.[13] A zinc catalyzed method derived from the deprotection of alcohols has been described involving zinc catalyzed activation of Si-O bonds to generate esters and chlorosilanes.[14] Chlorination of silanols has likewise generated interest due to the poor atom economy associated with silicon-based protecting group chemistry. Methods for recycling silanols back to the corresponding chlorosilanes have been published based on the use of acetyl chloride,[15] thionyl chloride[16] and phosphorous pentachloride.[17] Furthermore, palladium chloride can be used for catalytic activation of Si-OR, Si-OH and Si-H bonds in a biphasic system containing concentrated hydrochloric acid and hexane to provide the corresponding chlorosilanes.[18]



Scheme 2.3. Monochlorination of silanes.

For selective monochlorination of silanes (R_2SiH_2), illustrated in Scheme 2.3, only a few viable methods have been described earlier. Tin tetrachloride has been reported to chlorinate organosilanes in dibutyl ether providing the desired chlorosilanes upon precipitation of tin dichloride from the reaction media.[19] A less toxic method for monochlorination has been based on the use of stoichiometric copper chloride in combination with catalytic amounts of copper iodide.[20] Methods for halogenation of silanes and the applications of halosilanes have also been briefly reviewed and further developed by Kunai and Ohshita.[21]

2.2. Methodological Aspects[II]

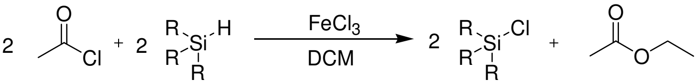
The kinetic experiments in the present work were carried out at ambient pressure at room temperature (23±1°C) using a magnetic stirrer. Dichloromethane (5 mL) was used as the solvent and 1.26 mol/L concentration of triphenylsilane or triisopropylsilane reagent was applied in all experiments.

All calculations were performed in Jaguar[22] using B3LYP-D3/LACVP*. The B3LYP-D3 functional combines the original B3LYP functional [23] with corrections for dispersion interactions.[24] The LACVP* basis uses the 6-31G* basis set for light elements, and the Hay-Wadt ECP with accompanying basis set for Fe.[25] Stationary points were validated by frequency calculations, and transition states were further validated by QRC[26] calculations. Energies in solvent were calculated with the PBF method[27] using parameters for dichloromethane. Final free energies were calculated by adding the thermodynamic corrections from the frequency calculation to the calculated free energies in solvent.

Estimation of the kinetic parameters was carried out by nonlinear regression analysis by using the simulation and parameter estimation software MODEST.[28] Ordinary differential equation (1) was solved with the backward difference method implemented in the software ODESSA,[29] which is based on the LSODE[30] code. All sets of experimental data, containing the concentrations as a function of time, were merged together. The sum of residual squares (Q) was minimized with the hybrid Simplex-Levenberg-Marquardt method.

$$Q = \left\| y_{\mathrm{exp}} - y_{\mathrm{est}} \right\|^2 = \sum_{\mathrm{k=1}}^{\mathrm{nsets}} \sum_{\mathrm{j=1}}^{\mathrm{nobs(k)}} \sum_{\mathrm{i=1}}^{\mathrm{nydata(j,k)}} (y_{\mathrm{exp,ijk}} - y_{\mathrm{est,ijk}})^2 \tag{1}$$

2.3. Results and Discussion

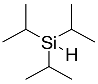
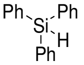
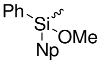


Scheme 2.4. $FeCl_3$ catalyzed chlorination of silanes with acetyl chloride as the chlorinating agent.

In search of more robust catalysts for the chlorination reaction, we turned our attention to Fe(III)-based systems. Inspired by the methodology reported by Voronkov et al.[5] for ester synthesis using silanes as reducing agents, the readily available $FeCl_3$ was selected as the catalyst and acetyl chloride (1.5 eq.) as the chlorine source. The reaction is illustrated in Scheme 2.4. After rapid solvent and chloride donor screening, $FeCl_3$ in dichloromethane for silanes (Si-H) and in dichloroethane for alkoxy silanes (Si-OR), in combination with acetyl chloride, was identified as a highly promising catalyst system. The initial results from the Fe-catalyzed reactions are summarized in Table 2.1.

While, unexpectedly, THF appeared as a promising solvent for the naphthyl containing methoxysilane, strong gelation under the reaction conditions employed was observed. This might be due to coordination of the iron species to the cyclic ether solvent, similar to the previously published method for cleavage of ethers with $FeCl_3$-based system, although ring opening of THF was not observed in our further test reactions.[31] As the purification methods used for these compounds are limited due to the risk of further reactions to silanol or siloxane, the use of THF as solvent was not investigated further. In all solvents screened for the naphthyl substituted silane (Table 2.1), except in THF, slow cleavage of the naphthyl group was observed during the chlorination reaction. Furthermore, the reaction of the *rac*-naphthyl substituted silane in toluene showed significant dimerization to siloxane.

Table 2.1. $FeCl_3$ (4 mol-%) catalyzed chlorination of silanes with acetyl chloride (1.5 eq) as the chlorinating agent.

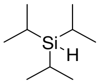
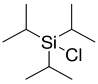
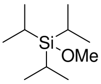
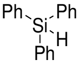
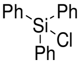
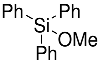
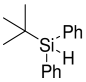
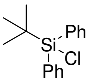
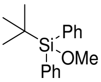
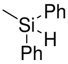
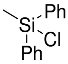
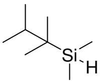
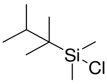
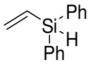
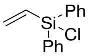
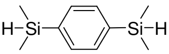
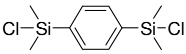
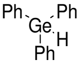
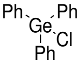
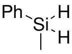
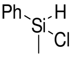
Substrate	**Solvent and Conversion to Chlorosilane**[a]			
	DCM	THF	DCE	Toluene
	93%	0%	99%	57%
	92%	0%	98%	15%
	79%[b]	100%[c]	79%[b]	30%[d]

[a] Conversions were determined after 24 hours by GC-fid. [b] Significant cleavage of naphthyl substituent was observed (~21 %). [c] Strong chelation observed. [d] Formation of large amounts of siloxane.

Following the conditions identified in the initial screening for chlorination reaction, a brief investigation of the substrate scope was carried out with the data collected in Table 2.2. Under these conditions, in most cases, solvents and starting materials could be used as such without additional purification. Likewise, extensive protection from atmospheric moisture was not required. For all methyl substituted silanes, excluding the Entry 6 in Table 2.3, evacuation of air and moisture is recommended in order to avoid catalytic siloxane formation in the presence of

$FeCl_3$. Nevertheless, small amounts of siloxane were detected in all of the reactions, in particular with compounds containing only phenyl and methyl substituents (Entries 7, 8 and 12 in Table 2.2 and Entries 2, 7 and 8 in Table 2.3)

Table 2.2. $FeCl_3$ catalyzed chlorination of silanes.[a]

Entry	Substrate	Catalyst loading (mol-%)	Solvent	Time (h)	Product	Yield[b] (%)
1		2.0	DCM	24	**1** 	63
2		0.5	DCE	24	**1**	88
3		2.0	DCM	24	**2** 	80
4		0.5	DCE	24	**2**	90
5		2.0	DCM	24	**3** 	69
6		2.0	DCE	72	**3**	86
7		2.0	DCM	24	**4** 	61
8		2.0	DCM	3	**5** 	58
9		2.0	DCM	24	**6** 	68
10		2.0	DCE	2	**7** 	90
11		2.0	DCM	24 h	**8** 	73
12		2.0[c]	DCM	24 h	**9** 	59[d]

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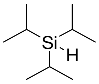
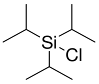
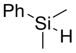
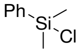
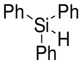
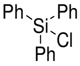
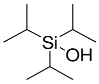
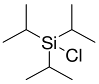
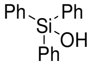
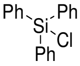
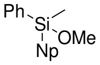
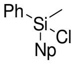
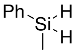
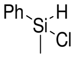
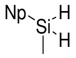
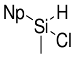
[a] General conditions: 6 mmol silane with acetyl chloride (1.5 eq.) in 10 mL of DCM or DCE at r.t. [b] Isolated yield. [c] $Fe(acac)_3$ used as catalyst.[d] Yield for monochlorinated product when using 1.1 eq. of acetyl chloride.

Depending on the steric constraints around the silicon atom, the reaction time varied from 2 to 72 hours by the use of 0.5-2% loading of the iron catalyst. Under ideal conditions, the $FeCl_3$ catalyst precipitated from the reaction mixture upon evaporation of the solvents, whereas for some compounds, especially in small scale, repeated filtrations through silica gel in order to remove all iron catalyst from the product were required, thereby decreasing the isolated yields. To furher expand the scope of the reaction, triphenylgermane was chlorinated in a similar manner in full conversion and with acceptable isolated yield after crystallization (Table 2.2, Entry 11).

Monochlorinations of methylphenylsilane (Table 2.2, Entry 12 and Table 2.3, Entry 7) and methyl-1-naphthylsilane (Table 2.3, Entry 8) were also investigated under similar conditions. In these reactions, $FeCl_3$ facilitated the rapid conversion of the starting material to the corresponding siloxane and significant cleavage of the silicon-naphthyl bond in case of methyl-1-naphthylsilane was observed. Switching of the catalyst to iron(III) acetylacetonate [$Fe(acac)_3$] in combination with 1.0 to 1.1 equivalent of acetyl chloride resulted in nearly quantitative conversions of the silanes with almost perfect selectivity towards the monochlorinated product at the expense of the reaction time. Also, in the case of methyl-1-naphthylsilane the use of $Fe(acac)_3$ as catalyst limited the cleavage of silicon-naphthyl bond.

Table 2.3. $FeCl_3$ catalyzed chlorination of silanes in 72-95 mmol scale with acetyl chloride (1.5 eq.) as the chlorinating agent.

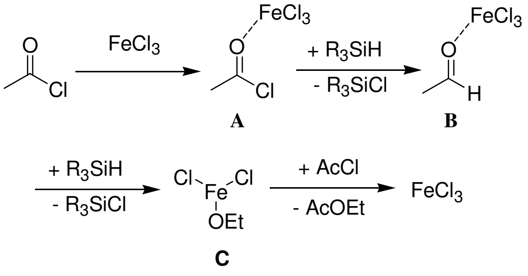
Entry	Substrate	Amount (mmol)	Catalyst loading (mol-%)	Solvent	Time (h)	Product		Yield[a] (%)
1		95	0.5	DCM	24	**1**		93
2		95	0.5	DCM	2	**10**		85
3		95	0.5	DCM	24	**2**		70
4		86	0.5	DCE	2	**1**		84
5		91	0.5	DCE	2	**2**		57
6		72	0.5	DCE	0.75	**11**		52[d]
7		82	2.0[b]	DCE	24	**9**		58[c,d]
8		82	1.0[b]	DCE	24	**12**		74[c,e]

[a] Isolated yield. [b] $Fe(acac)_3$ used as catalyst. [c] Yield for mono-chlorinated product. [d] 1.1. eq. of acetyl chloride [e] 1.0 eq. of acetyl chloride.

Almost full conversions were also obtained in 72-95 mmol scale, with the results for scale-up experiments collected in Table 2.3. Under these conditions, isolations and purifications could be carried out by distillation or crystallization, although it should be emphasized that, in particular when using triphenylsilane (Table 2.3, Entry 3) or tripehnylsilanol (Table 2.3, Entry 5) as the starting material, the crystallization conditions were far from optimized. Encouraged by the promising results obtained with alkoxy silanes, the method was also successfully expanded to incorporate silanols (Si-OH) as starting material under similar reaction conditions (Table 2.3. Entries 4 and 5).

2.4 Mechanism and Kinetics[II]

While a tentative catalytic cycle was initially suggested in publication **I**, it became apparent from the kinetic experimentation of the reaction that a significant revision of the reaction mechanism was required. The revised reaction mechanism is based on the oxophilicity of iron(III), and thus its potential function as a Lewis acid via coordination to oxygen in acetyl chloride. First, coordination of $FeCl_3$ to the acetyl chloride (**A** in Scheme 2.5) is suggested to take place, followed by reduction of the acid chloride to aldehyde (**B** in Scheme 2.5). Subsequent reduction of the coordinated aldehyde to ethoxide forms an ethoxylated catalyst species (**C** in Scheme 2.5), thus explaining the kinetic observations of catalyst deactivation to less active catalytic species. The ethoxylated catalyst can then be regenerated by acetyl chloride, releasing ethyl acetate.



Scheme 2.5. General reaction pathway used for the molecular modeling.

Based on the DFT calculations for the starting materials, intermediates and products, it appears obvious that the ethoxylated catalyst species [$FeCl_2(OEt)$, $FeCl(OEt)_2$ and $Fe(OEt)_3$] have significantly higher energy barriers for formation of the ionic intermediates, leading to catalyst deactivation. This observation further suggests that the ethoxylated catalyst species may be inert in the chlorination reaction, making the catalyst recovery cycle the most likely candidate for the rate determining step. A simplified potential energy surface for the species involved in the reaction was calculated and is presented in Figure 2.1.

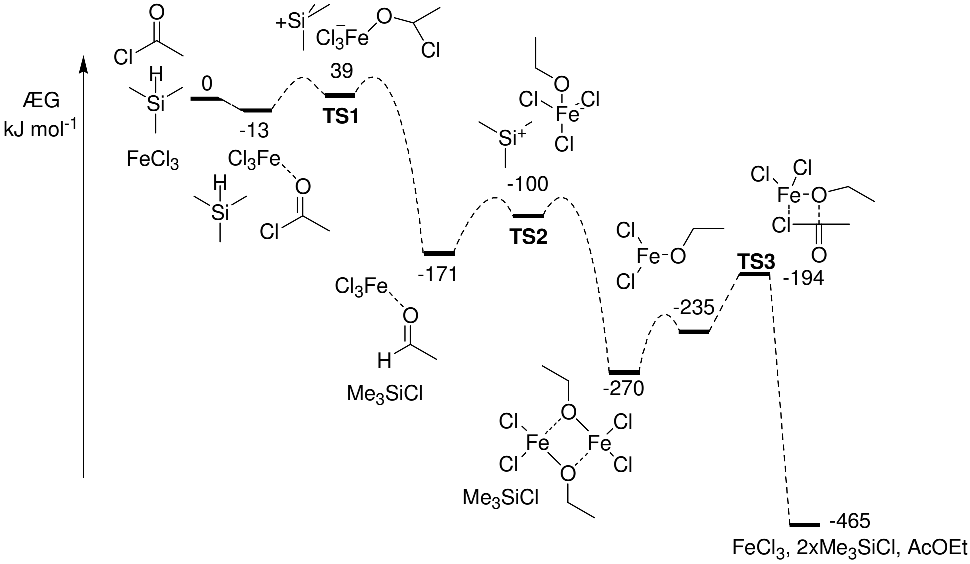
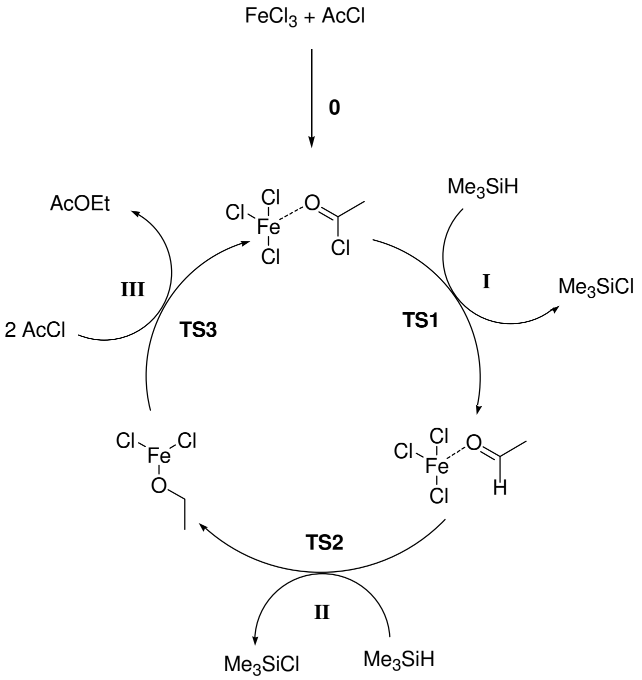


Figure 2.1. Full potential energy surface for the reactants, intermediates and products.

Each transition state was then further investigated with four and six-membered ring transition states for reduction of the acyl chloride and aldehyde, as well as for reactivation of the catalyst. Transition states leading to or from the ionic intermediates in **TS1** and **TS2**, however, can be shown to be barrierless when the hydride approaches the carbonyl or when the silyl cation approaches the chlorides. In kinetic sense such behaviour is characteristic for a diffusion-controlled reaction.[32] Since the potential energy surface does not have a maximum value, standard computational procedures for determination of the free energy barrier cannot be applied. However, as proposed earlier by Harvey and co-workers,[32] the free energy barrier for a diffusion-controlled reaction can generally be estimated to be ca. 20 kJ/mol. For comparison against the unimolecular barriers along the reaction paths, a concentration correction should be applied.



Scheme 2.6. Tentative catalytic cycle for the iron catalyzed chlorination of silanes.

As the concentration of the Lewis acid will be lower than standard state of 1 M, the barrier increases by approximately 6 kJ/mol for each order of magnitude of the concentration lowering. Under the experimental conditions applied the Lewis acid concentration was approximately 0.01 M while the computational investigation assumes 1.0 M reaction conditions. Consequently, the free energy barriers for **TS1** and **TS2** had to be increased by approximately 12 kJ/mol, yielding an overall barrier of ~ 32 kJ/mol. Following the DFT calulation (Figure 2.1. and Scheme 2.5.) a catalytic cycle was drawn for the kinetic modeling, illustrated in Scheme 2.6.

The four reactions involved are indicated with the numbering **0**, **I**, **II** and **III**, as shown in Scheme 2.6. Reaction **0** is considered to be irreversible and rapid, reactions **I** and **II** are irreversible and reaction **III** is considered to be reversible. The formation of ethyl acetate is considered to decrease the reaction rate of the overall cycle.

$$A = R_3SiH \tag{2}$$
$$B = AcCl \tag{3}$$
$$C = AcOEt \tag{4}$$

Thus the rate equation based on Scheme 2.6 takes the form:

$$r = \frac{k_{1''}AB^2}{k_{2''}B^2 + k_{3''}C + A}C_{cat} \tag{5}$$

The overall fit of the final model to the experimental data can be represented with the R^2 values, which are 96.53% for triphenylsilane and 94.61% for triisopropylsilane. The values for the rate constants are collected in Table 2.4.

Table 2.4. The parameter values and standard errors obtained for triphenylsilane and triisopropylsilane.

	Triphenylsilane (R^2 = 96.53%)		Triisopropylsilane (R^2 = 94.61%)	
Parameter	Value	Std. Error (%)	Value	Std. Error (%)
$k_{1''}$	34.6	11.5	20.4	18.3
$k_{2''}$	~0	-	0.414	43.4
$k_{3''}$	1.95	21.1	0.89	33.1

The parameter values were obtained by allowing the parameters to freely find their optimum value when the objective function was minimized. In case of triphenylsilane the parameter $k_{2''}$ was assigned a very low value, which results in $k_{2''}B^2 << k_{3''}C+A$ in eq. 5. The results clearly show that the standard errors of the parameters are sufficiently low. The fit of the models to experimental data (Figure 2.2. and Figure 2.3.) can be considered adequate for the complex overall reactions, as the R^2 values in Table 2.4 indicate.

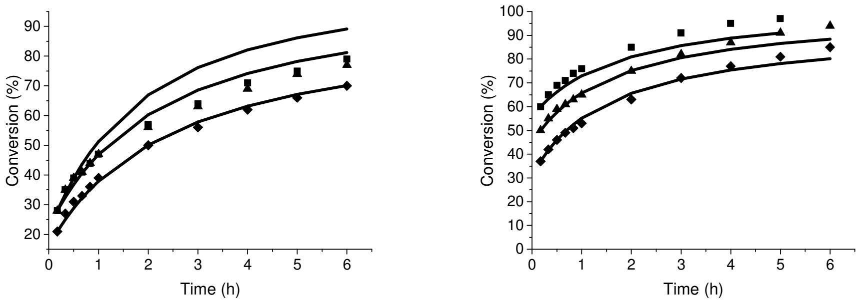


Figure 2.2. Conversion of triisopropylsilane against time using 1.0 (left) and 2.0 (right) mol-% of $FeCl_3$ with various amounts of acetyl chloride. Experimental data noted as dots (AcCl 1.5 eq. ■; AcCl 1.25 eq ▲; AcCl .1.0 eq ◆) and model as a line.

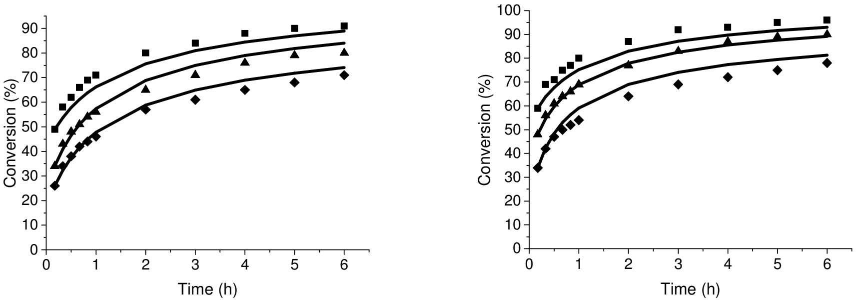


Figure 2.3. Conversion of triphenylsilane against time using 1.0 (left) and 2.0 (right) mol-% of $FeCl_3$ with various amounts of acetyl chloride. Experimental data noted as dots (AcCl 1.5 eq. ■; AcCl 1.25 eq ▲; AcCl .1.0 eq ◆) and model as a line.

The fit of the model to experimental data can be improved by adding an extra cycle to the mechanism, between steps **II** and **III** in Scheme 2.6, due to an experimental observation of aldehyde release when the reaction was carried out using hexanoyl chloride instead of acetyl chloride as the chlorinating agent. This raises the number of parameters to statistically unacceptable level, but the formed ethyl acetate (**III** in Scheme 2.6) can mathematically also be considered to be partly acetaldehyde as the formation of both compounds is a reversible reaction, which decreases the overall reaction rate and thus cannot be well differentiated from each other within the experimental data set collected.

2.5. Summary and Conclusions

A versatile and economically viable method for the chlorination of silanes, silyl alkoxides, and silanols, tolerant of a variety of substituents, and including monochlorination of silanes (R_2SiH_2) was developed. Limitations and challenges arise particularly in the cases of methyl and naphthyl containing silyl compounds, where siloxane formation and cleavage of the silicon−naphthyl bonds were observed. While the prolonged storage of Fe(III) chloride may be problematic due to its sensitivity toward light and moisture, Fe(acac)$_3$ can be used as a substitute in most cases at the expense of prolonged reaction times. The Fe(acac)$_3$ system is also less prone to cleave the silicon−naphthyl bonds in the substrates thus making it optimal in such cases.

Mechanism of the chlorination of silanes using FeCl$_3$ as the catalyst and acetyl chloride as the chlorinating source was studied in detail. Based on the experimental observations, DFT calculation and kinetic modeling, the overall reaction was shown to proceed involving at least two reaction cycles. Moreover, the results show that the formation of ethyl acetate and acetaldehyde can be considered to be reversible influencing strongly the overall reaction rate. Unfortunately a full elucidation of such mechanism would require a very complex rate equation with statistically unsound number of parameters. Thus a more simple single cycle model incorporating the main features was used to decrease the model complexity yielding adequate correlation with experimental data.

2.6. References

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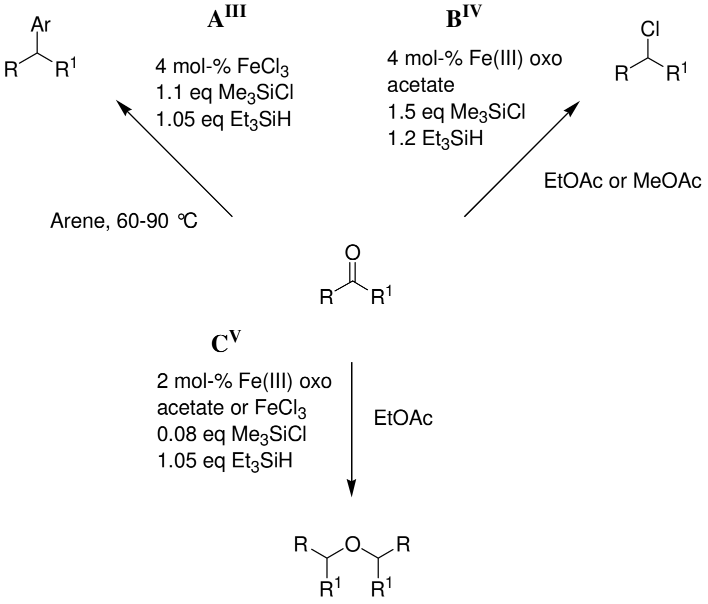
3. IRON CATALYZED TRANSFORMATIONS OF KETONES, ALDEHYDES AND ALCOHOLS MEDIATED BY ORGANOSILANES



Scheme 3.1. Iron catalyzed benzylation (**A**), iron catalyzed chlorination (**B**) and iron catalyzed reductive etherification (**C**).

This Chapter covers three different transformations from similar starting material and reagents, that can be directed to desired direction by choice of solvent, catalyst, temperature or by manipulating the amount of chlorotrimethylsilane used in the reaction. While $FeCl_3$ in principle functions as the catalyst for every transformation described in this Chapter, in some cases the use of iron(III) oxo acetate was adapted in order to limit side reactions, for example Friedel-Crafts alkylation in reactions **B** and **C** described in Scheme 3.1. All of the reactions presented here bear a likeness to that of other reactions using silanes as reducing agents.[1] Also, similar reactions have been studied extensively in recent years by Sawama and coworkers.[2]

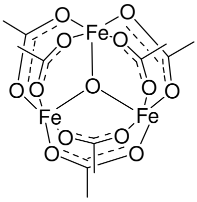


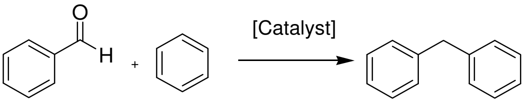
Figure 3.1. Tentative structure for iron(III) oxo acetate.

In Chapters 3.2 and 3.3 atmospherically oxidized iron(II) acetate, here denoted as "iron (III) oxo acetate", was used as catalyst. This catalyst is most likely a trinuclear iron complex with central oxygen atom bridging three iron(III) molecules, tentatively illustrated in Figure 3.1. Such trinuclear metal acetate complexes have been investigated earlier and while structural features have been proposed, definite proof of the exact structure for this particular complex has not been presented.[3]

3.1. Iron Catalyzed Benzylation of Arenes[III]

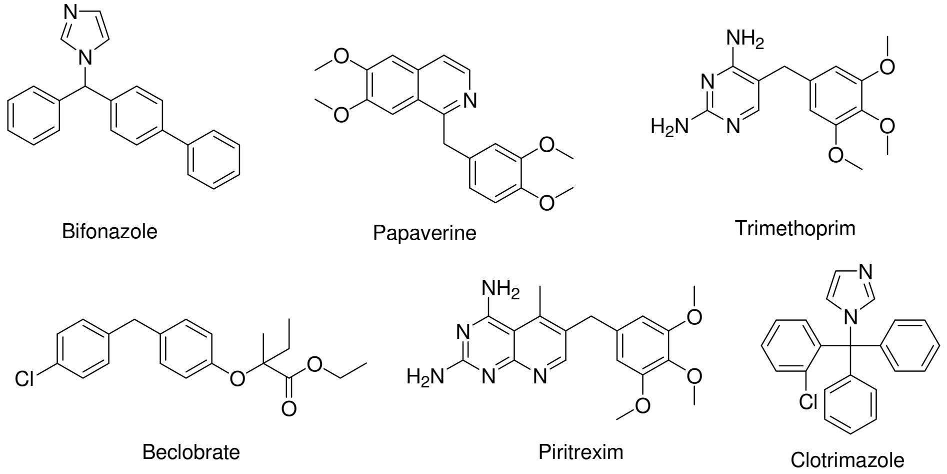
3.1.1. Introduction

While the direct use of carbonyl compounds as alkylating agents in Friedel-Crafts alkylations is attractive, illustrated in Scheme 3.2, such reactions often suffer from low yields and undesirable side product formation as a result of multiple alkylations.[4] Acid catalyzed reductive Friedel-Crafts reaction between benzaldehyde and benzene has been known since 1886,[5] typically to yield a mixture of products in low yields.[6]



Scheme 3.2. Reductive Friedel-Crafts benzylation.

During the past 15-20 years, the field of catalytic benzylation reactions has expanded remarkably. In recent investigations, frequently utilized benzylating agents have included acetylated or trimethylsilylated benzylic alcohols,[2e,7] styrene derivatives,[8] benzyl alcohols[9] and benzyl thiocyanates.[10] Also underivatized alcohols have been used for Friedel-Crafts reaction with $FeCl_3$ and in combination with silver hexafluoroantimonate ($AgSbF_6$),[11] as well as with ionic liquid supported iron(III) triflate [$Fe(OTf)_3$].[12] This type of methodology can be readily used for production of fine chemicals, building blocks for pharmaceuticals or direct synthesis of pharmaceuticals. Representative examples of pharmaceutical targets that could be obtained by Friedel-Crafts chemistry are shown in Figure 3.2.



Bifonazole Papaverine Trimethoprim

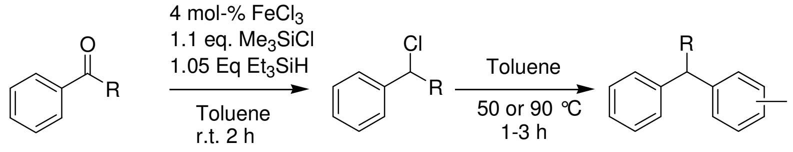
Beclobrate Piritrexim Clotrimazole

Figure 3.2. Possible pharmaceutical targets for reductive Friedel-Crafts chemistry.

One of the first examples of catalytic reductive Friedel-Crafts alkylations using ketones and aldehydes as reagents instead of preactivated alcohols with minimal side products utilized Ga_2Cl_4.[13] Subsequent reports used superacids,[14] and scandium(III) trifluoromethanesulfonate as the catalysts.[15] Following these approaches, the use of $InCl_3$[16] and $InBr_3$[17] as catalysts was reported. A reductive Friedel-Crafts reaction using $FeCl_3$ as the catalyst in the presence of dichloromethylsilane and thiophene as the nucleophile has likewise been reported.[18]

3.1.2. Results and Discussion

Previously, chlorodimethylsilane has been used as the source of chloride and hydride[16,18] to facilitate the formation of halogenated intermediate for the subsequent Friedel-Crafts reaction. In the present investigation with this type of methodology the use of chlorodimethylsilane yielded significant amounts of ethylbenzene as undesired side product and produced also dimethylsiloxanes with varying chain lengths. These in turn proved tedious or impossible to fully remove from the crude product. The selectivity issue was resolved by switching to the use of chlorotrimethylsilane as the chlorine source, followed by portionwise addition of a diluted triethylsilane solution at room temperature. By this methodology, formation of the corresponding 1-chloro-1-phenylethane intermediate was observed with concomitant suppression of the formation of undesired side product (ethyl benzene) and limited the formation of polysiloxane byproducts. Instead, only easily separable hexaethyldisiloxane and 1,1,1-triethyl-3,3,3-trimethyldisiloxane compounds were formed as byproducts.

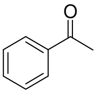
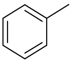
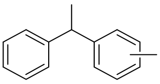
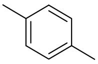
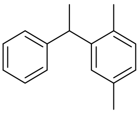
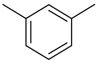
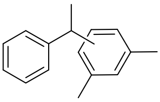
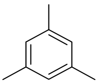
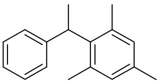
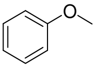
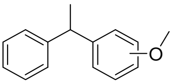
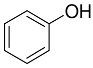
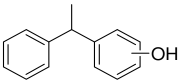
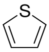
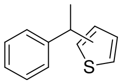
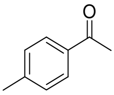
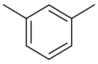
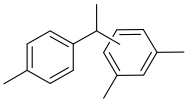
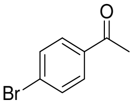
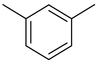
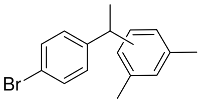
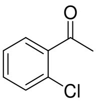
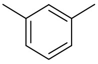
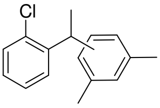


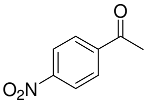
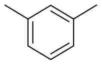
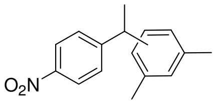
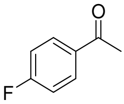
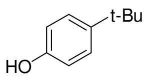
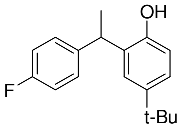
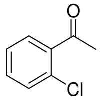
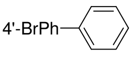
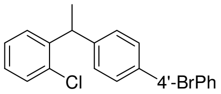
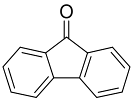
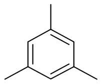
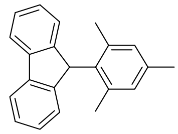
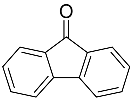
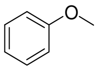
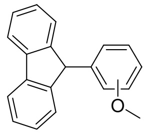
1

Scheme 3.3. One-Pot *in situ* reductive chlorination and Friedel-Crafts benzylation.

The halogenated intermediate could be formed at room temperature and the desired Friedel-Crafts alkylation took place at elevated temperatures between 50-90 °C. The general, optimized catalyst system used for substrate scope investigation is illustrated in Scheme 3.3 with results on the cascade-type chlorination-Friedel-Crafts alkylation sequence of benzylic ketones collected in Table 3.1 and the corresponding reactions using benzaldehydes as the electrophile shown in Table 3.2. For some starting materials further adjustments were necessary in order to suppress the potential side reactions, optimize the reaction yields and for isolation of the final products. Ideally, the arene reagents studied were also used as solvents.

Table 3.1. Substrate scope using benzylic ketones as electrophiles.[a]

Entry	Electrophile	Nucleophile	Time (h)		Product	Yield[b] (%)	Selectivity[c] o:m:p/2:3
1			5	**1**		78	7:1:92
2			3[e]	**2**		66	-
3			3	**3**		94	tr:0:100
4			3[e]	**4**		68	-
5			3	**5**		86	tr:0:100
6			3[f]	**6**		57	30:0:70[d]
7			4	**7**		81	81:19
8			3	**8**		69	3:0:97
9			3	**9**		87	tr:0:100
10			3	**10**		97	tr:0:100

11			5	**11**		87	13:1:86
12			4[f]	**12**		23	-
13			4[f]	**13**		76	-
14			7	**14**		94	-
15			3	**15**		93	36:0:64[d]

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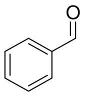
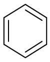
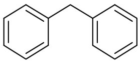
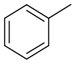
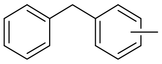
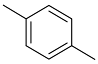
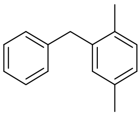
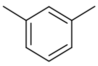
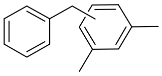
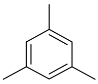
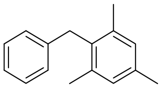
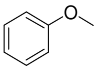
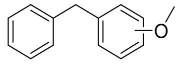
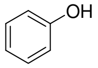
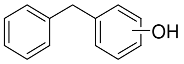
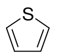
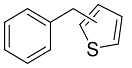
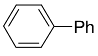
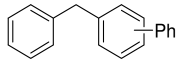
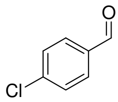
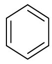
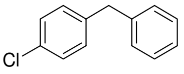
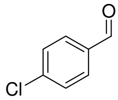
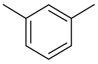
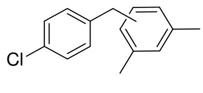
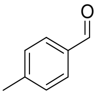
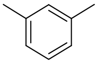
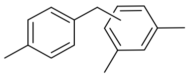
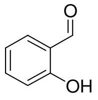
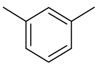
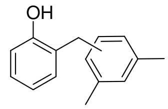
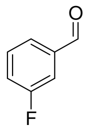
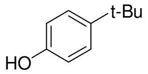
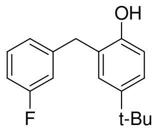
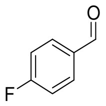
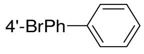
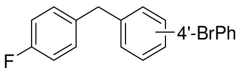
[a] General reaction conditions: Arene reagent used as solvent unless mentioned otherwise; Et_3SiH was diluted to 1 mL volume with the corresponding arene or dichloromethane solvent and added portionvise at the rate of 0.1 mL/5 min at r.t. during 2h after which the temperature was raised to 50 °C unless noted otherwise. [b] Isolated yield for the mixture of isomers unless noted otherwise. [c] Determined by GC-MS; tr = trace. [d] Both isomers isolated and characterized separately. [e] Reaction temperature 90 °C. [f] Dichloromethane used as the solvent.

In accordance with the general trends of substituent effects in electrophilic aromatic substitution reactions, the formation of *ortho- meta-* and *para*-isomers were observed. However, as could be expected, competition between the first formed 1-chloro-1-phenylethane intermediate and the added arene nucleophile took place. In cases where the intermediate and nucleophile had similar reactivities, tendency towards dimerization and potential oligomerization was observed and thus reduced the overall yield of the desired product. This was particularly the case with the reactions of acetophenone with benzene and phenyl bromide, where in the first reaction very little and in the latter case none of the desired coupling product was observed.

Accordingly, a careful selection of the reagents was necessary for optimization of the reaction yields and regioselectivities. While the best results and yields were obtained by use of up to ten-fold excess of the arene nucleophile as the solvent, also close to equivalent concentrations of the arene reagent were briefly screened with variable results (Entries 6, 12 and 13 in Table 3.1; and Entries 7, 9, 14 and 15 in Table 3.2). As a potential route for preparation of e.g., cyclopentadienyl-type ligand precursors for transition metal complexes, two experiments were carried out using fluorenone as the starting material (Entries 14 and 15 in Table 3.1) providing good yields but only mediocre regioselectivities.

Table 3.2. Substrate scope using benzaldehydes as electrophiles.[a]

Entry	Electrophile	Nucleophile	Time (h)		Product	Yield[b] (%)	Selectivity[c] o:m:p/2:3
1			4[f]	**16**		40	-
2			24[f]	**17**		48	42:5:53
3			3[f]	**18**		78	-
4			3	**19**		76	18:0:82
5			3[e,f]	**20**		80	-

6			6[e]	**21**		81	37:0:63[d]
7			4[e,g]	**22**		62	48:0:52[d]
8			6[e]	**23**		50	63:37
9			5[e,g]	**24**		70	53:1:46
10			4	**25**		68	-
11			3	**26**		72	13:tr:87
12			3	**27**		91	13:0:87
13			3	**28**		39	5:0:95
14			24[e,g]	**29**		23	-
15			6[e,g]	**30**		51	44:0:56[d]

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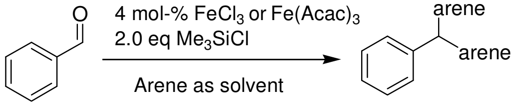
[a] General reaction conditions: Arene reagent used as the solvent unless mentioned otherwise; Reaction temperature 50 °C; Et_3SiH was diluted to 1 mL volume with the corresponding arene or dichloromethane solvent and added portionwise at the rate of 0.1 mL/5 min. [b] Isolated yield for the mixture of isomers unless noted otherwise. [c] Determined by GC-MS; tr = trace. [d] Both isomers isolated and characterized separately. [e] Reaction commenced at r.t. [f] Reaction temperature 90 °C. [g] Dichloromethane used as the solvent.

In general, the benzaldehyde derivatives studied proved slightly less reactive than the corresponding acetophenones, resulting also in poor regioselectivities in terms of the *ortho*-, *meta*- and *para*-isomers formed. In strong contrast to the corresponding reaction with acetophenone (Table 3.1, Entry 1), the reaction of benzaldehyde with toluene (Table 3.2, Entry 2) was very slow, resulting in <50 % isolated yield, while the reaction with benzene (Table 3.2, Entry 1) proceeded without extensive side product formation and within reasonable time frame. Notably, in accordance with literature precedence,[19] formation of ethers from benzaldehydes was observed. The ethers formed could be converted to the corresponding chlorides by further heating of the reaction mixture with further conversion to form the desired diarylmethane.

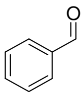
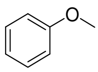
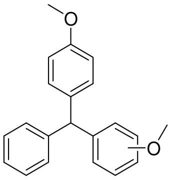
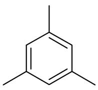
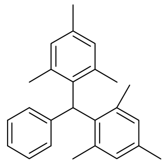
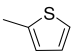
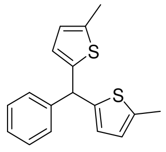
The compounds **24** and **25** (Table 3.2, Entries 9 and 10), in turn, could be considered as potential precursors for bifonazole and antihistamine synthesis, such as cetirizine (Figure 3.2). Unfortunately, particularly with the compound **24** (Table 3.2, Entry 9), where selectivity towards the *para*-isomer would be desired for potential use as a pharmaceutical intermediate, significant *para*-selectivity was not observed.



Scheme 3.4. Diarylation of benzaldehyde

When using highly electron rich arenes, such as mesitylene, anisole or thiophene as the nucleophile with benzaldehyde, formation of triarylmethanes as side products was observed, illustrated in Scheme 3.4. While the reaction conditions for Entries 5, 6 and 8 in Table 3.2 were optimized for primarily yielding the corresponding diarylderivatives **20**, **21** and **23**, the conditions were also optimized towards the formation of the triarylmethanes, similarly to an earlier published method.[20] Here, it was observed that the use of $FeCl_3$ as the catalyst, together with at least two-fold excess of chlorotrimethylsilane at elevated temperatures, resulted in diarylation of the benzaldehyde used. The results are collected in Table 3.3.

Table 3.3. Synthesis of triarylmethanes.

Entry	Electrophile	Nucleophile	Time (h)		Product	Yield[a] (%)	Selectivity[b] o:m:p/2:3
1			5[c]	**31**		99	12:0:88
2			6[c]	**32**		33	-
3			0.5[d]	**33**		96	-

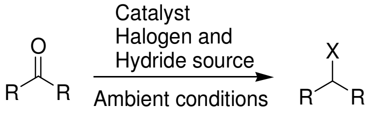
[a] Isolated yield for the mixture of isomers unless noted otherwise. [b] Determined by GC-MS [c] Reaction temperature 90 °C. [d] Reaction carried out at rt using $Fe(acac)_3$ as catalyst.

The use of anisole under similar conditions (Table 3.3, Entry 1) provided a high yield at the expense of regioselectivity. For reaction of benzaldehyde with mesitylene to yield the corresponding triarylmethane **32** (Table 3.3, Entry 2), various reaction conditions were screened resulting in poor yields only, without complete selectivity towards the desired triaryl compound **32**. Fortunately, in this case the undesired diaryl compound could be separated from the reaction mixture by washing with cold ethanol. When the same reaction was attempted with thiophene, the use of $FeCl_3$ as the catalyst resulted in oligomerization of the diarylated product only, due to significant increase in reactivity of the substituted thiophene. Also, the use of $FeCl_3$ resulted in some degree of polymerization of the thiophene making the purification tedious. The use of $Fe(acac)_3$ as the catalyst instead of $FeCl_3$, in this case, suppressed the side reactions, including thiophene polymerization. Consequently, the reaction with 2-methylthiophene was repeated with $Fe(acac)_3$ as the catalyst providing the desired triarylmethane **33** (Table 3.3, Entry 3) in excellent yield.

3.2. Iron Catalyzed Halogenation of Benzylic Ketones, Aldehydes and Alcohols[IV]

3.2.1. Introduction

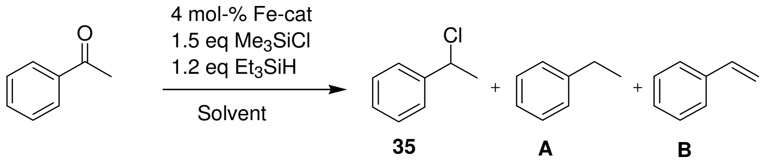
Carbonyl compounds play key roles in organic synthesis as products, intermediates and reagents. Typically, deoxygenative chlorination of carbonyl compounds is a multistep process, involving reduction of the carbonyl group to an alcohol, followed by chlorination with thionyl chloride or phosphorus pentachloride.[21] Such procedures often use harsh reaction conditions and require careful synthesis planning in order to mask all other reactive functionalities in the molecule. A clear demand exists for potential one-step or one-pot reactions at ambient temperatures under mild reaction conditions. A general example of such reaction is illustrated in Scheme 3.5.



Scheme 3.5. Reductive halogenation of carbonyl compound.

Metal compounds, such as organoaluminium halides have been reported to transfer halogen atoms to carbonyl groups, but the method suffers from the use of stoichiometric amounts of the aluminium reagent resulting in poor selectivity towards the halogenated product.[22] A related one pot method utilizes stoichiometric amount of titanium tetrachloride in combination with trimethylsilyl cyanide, providing α-halonitriles.[23] Also, in the reduction of ketones with halogenated borane compounds, reductive halogenation of some acetophenones has been observed.[24] Furthermore, 1,1,3,3-tetramethylsiloxane, together with chlorotrimethylsilane in the presence of sodium iodide or lithium bromide, has been reported to reductively halogenate aromatic carbonyl compounds.[25] Other similar examples include Lewis-acid catalyzed processes in the presence of indium(III) hydroxide[26] or $FeCl_3$.[27] In these cases, chlorodimethylsilane (Me_2SiHCl) and dichloromethylsilane ($MeSiHCl_2$) were used as the chlorine and hydride sources respectively. Recently, iron catalyzed transformations of trimethylsilyl derivatized alcohols to azides with trimethylsilyl azide have been reported.[2a]

3.2.2. Results and Discussion



Scheme 3.6. General conditions for chlorination of acetophenone.

Similar to the earlier reports on catalytic halogenation,[26,27] benzylic aldehydes and ketones were selected as starting material. While similar reactions have been published with $FeCl_3$ as the catalyst at elevated temperature,[27] the present investigation was aiming for reaction at room temperature. Consequently, for initial reaction optimization and screening, $FeCl_3$ was employed as the catalyst (Scheme 3.6). The amounts of silanes used, 1.5 equivalents of chlorotrimethylsilane and 1.2 equivalents of triethylsilane, were adapted from the previous investigation on benzylation of arenes, (see Chapter 3.1). First, a solvent screening was carried out in order to investigate the influence of reaction media on the product distribution between the fully reduced ethylbenzene derivative (**A**) and the desired (1-chloroethyl)benzene (**35**) in the chlorination of acetophenone. In order to minimize side product formation from competing Friedel-Crafts alkylation, aromatic solvents were excluded from the study. The results are summarized in Table 3.4. In addition to the reduction side product **A**, formation of small amounts of styrene (**B**) was observed. A significant influence of the solvent on the reaction outcome and product distribution was nevertheless evident. For example, in both dichloromethane and ethyl acetate the chlorination reactions are completed within one hour while significantly larger amounts of the side product **A** are formed in the former solvent.

Table 3.4. Influence of solvent on the reductive chlorination of acetophenone using $FeCl_3$ as the catalyst.

Solvent	Time(h)	Conversion(%)	Selectivity **35**:**A**:**B**
DCM	1	96	75:25:0
Hexane	24	99	96:3:1
EtOAc	1	>99	97:3:0
DEE	24	92	95:3:2
THF	24	92	92:8:0
ACN	24	59	48:52:0

Table 3.5. Influence of catalyst (4 mol-%) on the conversion and product distribution in the reductive chlorination of acetophenone in ethyl acetate.

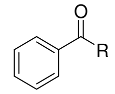
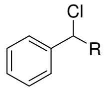
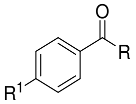
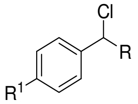
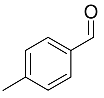
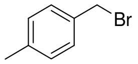
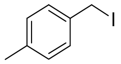
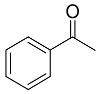
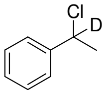
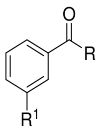
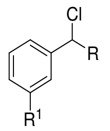
Catalyst	Time(h)	Conversion(%)	Selectivity **35**:**A**:**B**
$FeCl_3$	4	>99	98:1:1
$Fe(acac)_3$	4	97	96:3:1
$Fe(ClO_4)_3xH_2O$	4	90	97:2:1
$Fe(ClO_4)_2xH_2O$	4	99	97:2:1
Fe(III) oxo acetate	1	>99	97:2:1

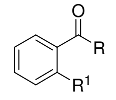
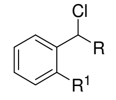
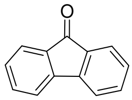
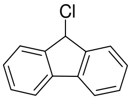
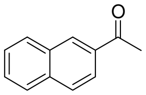
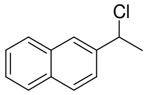
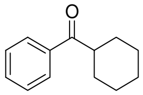
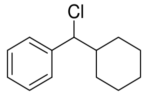
Next, also other readily available iron (pre)catalysts were investigated in an effort to replace $FeCl_3$, and to further minimize the risk of Friedel-Crafts alkylation as a side reaction The obtained data is presented in Table 3.5. Both iron(II) chloride and acetate were investigated, but due to very slow reactivities and solubility issues they were not investigated further. It is also likely that iron(II) perchlorate is rapidly oxidized to iron (III) species under the employed reaction conditions. Based on the results, iron(III) oxo acetate was selected for further experiments due to its ease of handling, preparation from readily available iron(II) acetate by heating, simple storage and consistent catalytic performance.

Following the results obtained from solvent and catalyst screening, the substrate scope of the halogenation methodology was investigated using iron(III) oxo acetate as the catalyst in ethyl acetate. The results are collected in Table 3.6. For all substrates, moderate to high conversions were reached with the isolated yields ranging from 41-98%. In general, electron donating substituents, such as alkyl and phenyl (Table 3.6, Entries 1, 3-5, 15, 16, 20), were well tolerated on aromatic aldehydes. For aromatic ketones, electron withdrawing substituents, including halides, were well tolerated (Table 3.6, Entries 2, 6-10, 21), whereas for compounds containing electron donating groups, some optimizations to the reaction conditions were required. In such cases (Table 3.6, Entries 18 and 23) reduced temperature and portionwise addition of triethylsilane was necessary.

The further applicability of the method for bromination and iodination was briefly investigated using bromotrimethylsilane and iodotrimethylsilane as the halide donors. With 4-methylbenzaldehyde as the starting material, the corresponding bromo (**48**) and iodo (**49**) products were formed in 95% and 71% yields, respectively (Table 3.6, Entries 15-16). Furthermore, a successful scale-up experiment was performed with iodotrimethylsilane at 16 mmol (~1.9 g) scale (Table 3.6, Entry 16), followed by upscaling with 4’-chloroacetophenone (Table 3.6, Entry 7) to 85 mmol scale in acceptable yield. Finally, also the use of deuterotriethylsilane for in situ halogenation/deuterium labelling of the benzylic position was investigated (Table 3.6, Entry 17) yielding results comparable to those obtained with triethylsilane (Table 3.6, Entry 2).

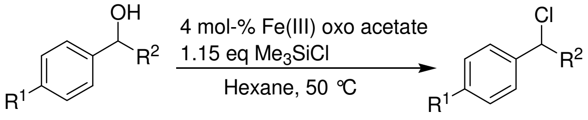
Table 3.6. Substrate scope.[a]

Entry	Substrate	R	R_1	Time (h)		Product	Yield[b] (%)
1		H	-	24	**34**		52
2		Me	-	1	**35**		83
3		H	4-Me	2	**36**		98
4		H	$C(CH_3)_3$	1	**37**		79
5		H	4-Ph	3	**38**		52
6		Me	4'-CF3	2	**39**		56
7		Me	4'-Cl	1	**40**		69[c]
8		Me	4'-Br	2	**41**		85
9		Me	4'-F	1	**42**		81
10		Me	COOEt	1	**43**		82
11		Et	H	1.5	**44**		92
12		Bu	H	2	**45**		96
13		$(CH_2)_3Cl$	4'-F	1	**46**		66
14		$C(CH_3)_3$	H	5	**47**		98
15		-	-	1	**48**		95[d]
16		-	-	0.5	**49**		71[e]
17		-	-	1	**50**		80[f]
18		Me	3'-Me	4	**51**		80
19		Me	3'CN	5	**52**		40

20		H	2-Me	1	**53**		85
21		Me	2'-Cl	2	**54**		96
22		-	-	3	**55**		69
23		-	-	3.5	**56**		41
24		-	-	2	**57**		71

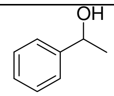
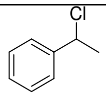
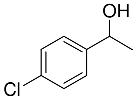
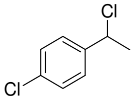
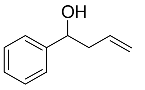
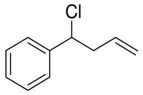
[a] Reaction conditions (unless specified otherwise): 4-10 mol% of Fe(III) oxo acetate as the catalyst, 1.5 eq. of Me_3SiCl as the chlorination agent, 1.05-1.2 eq. of Et_3SiH in AcOMe or AcOEt at r.t. [b] Isolated yield. [c] Reaction performed on 85 mmol scale with ethyldimethylsilane as the hydride source. [d] With Me_3SiBr as the halogenation agent in AcOMe. [e] With Me_3SiI as the halogenation agent in AcOEt. [f] With Me_3SiCl as the halogenation agent in combination with 1.2 eq. of Et_3SiD in MeOAc.

Incorporation of nitro or cyano substituents to the benzene ring resulted in significant dimerization/oligomerization via Friedel-Crafts alkylation resulting in very poor isolated yields for the halides. In case of *meta*-cyano substituted acetophenone derivative (Table 3.6, Entry 19), good conversion and acceptable selectivity towards the chlorinated product **52** was observed, but only mediocre isolated yield of 40% was obtained. Both acetophenone and benzaldehyde derivatives containing substituents that strongly activate the aromatic ring for electrophilic aromatic substitution, such as methoxy or hydroxyl groups, resulted in poor selectivity towards the desired halide. This is due to side reactions, including the observed subsequent Friedel-Crafts alkylation and Clemmens-type reduction of the starting material. Also the use of free carboxylic acid, acetyl protected amine or amides as substituent proved problematic due to poor solubility in ethyl acetate, dichloromethane or chloroform. With ethyl benzoylacetate as the starting material, only decarboxylation resulting in acetophenone formation was observed.



Scheme 3.7. Chlorination of benzylic alcohols.

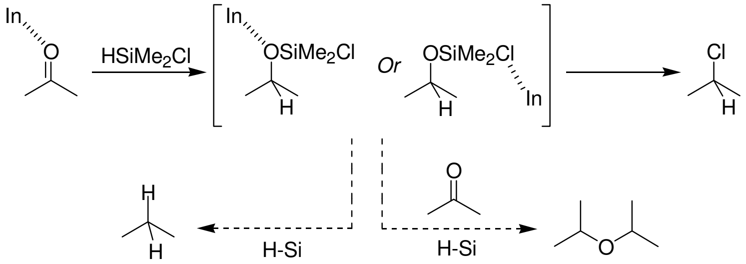
Table 3.7. Iron catalyzed halogenation of benzylic alcohols.[a]

Entry	Substrate	Time (h)		Product	Yield (%)[b]
1		1(4)[c]	**35**		81(90)[c]
2		1	**40**		68
3		1.5	**58**		71

[a] Reaction conditions 4 mol% of Fe(III) oxo acetate as the catalyst, 1.15 equiv. of Me_3SiCl as the chlorination agent in hexane at 50 °C. [b] Isolated yield [c] The yield and reaction time for the corresponding reaction on ~85 mmol scale with 1.0 mol-% of Fe(III) oxo acetate given in parentheses.

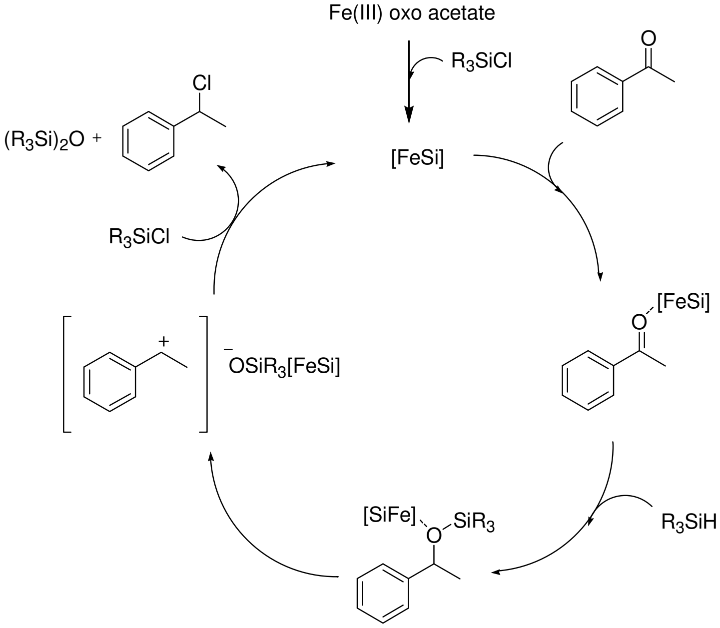
The methodology was further extended for halogenation of benzylic alcohols. The corresponding benzylic alcohol was reacted with slight excess of chlorotrimethylsilane in hexane using 4 mol-% of Fe(III) oxo acetate as the precatalyst (Scheme 3.7). At room temperature, the main product observed was the corresponding dimerized ether via condensation-type reductive etherification reaction (see Chapter 3.3). Subsequent heating to 50 °C, however, cleaved the ether to form the desired chloride. For these reactions, the use of esters as solvent resulted in the formation of small amount of side products due to transesterification, which could be eliminated by switching to hexane as the reaction medium. Selected examples are collected in Table 3.7.

3.2.3. Mechanism and Kinetics



Scheme 3.8. Original mechanism proposed by Baba and coworkers.[26]

Earlier Baba and coworkers have suggested a tentative mechanism for the Lewis acid catalyzed derivatization of carbonyl compounds, illustrated in Scheme 3.8.[16,26] In the present work, by using pivaloylphenone as the substrate for chlorination, formation of the corresponding silyl ether via hydrosilylation reaction was initially observed which then slowly converted to the desired chloride product. When enantiomerically pure (*R*)-1-phenylethanol was first silylated with chlorotrimethylsilane and then subjected to the general reaction conditions used, in the absence of triethylsilane, formation of fully racemic product was observed. Both of these observations are in line with the earlier mechanistic suggestion by Baba and coworkers.[16,26] Consequently, it is likely that the silyl chloride used here is first activated by iron(III) oxo acetate, similar to activation of InX_3 in earlier work.[28] Based on this hypothesis, a tentative catalytic cycle was developed, illustrated in Scheme 3.9.



Scheme 3.9. Tentative catalytic cycle for the chlorination reaction.

For further validation of the mechanism suggested here, kinetic investigation was carried out by varying the amounts of the catalyst, triethylsilane and chlorotrimethylsilane used. In the substrate scope examination it was observed that the reactions were exothermic. Thus, the amount of ethyl acetate in the test reactions on 2 mmol scale was increased to 5 mL, considerably slowing down the rate of the reaction either by lowering the initial heat release to minimal and possibly by limiting the coordination of acetophenone to the catalyst.

Based on the initial observations from the kinetic data collected, it became evident that the concentration of chlorotrimethylsilane does not influence the rate of the reaction as long as it is sufficient to run the reaction to full conversion. This was also verified by an experiment using the triethylsilylated intermediate directly, confirming a zero order reaction with respect to the concentration of the iron precatalyst. In contrast, an increase in the concentration of triethylsilane significantly influenced the rate of the reaction. If the chlorosilane would also take part in the active species of catalyst as has been previously postulated,[16a,16b,26,28] it could be expected that changing of the halide from chloride to bromide would influence on the rate of the reaction. This type of effect was indeed observed and is illustrated in Figure 3.3.

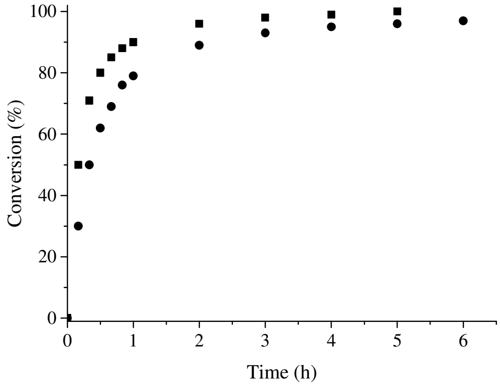


Figure 3.3. Conversion against time using 4.0 mol-% of Fe(III) oxo acetate with chloro trimethylsilane (●) and bromo trimethyl silane (■) as halide sources.

Experimental data for halogenation by varying the concentration of chlorotrimethylsilane are presented in Figure 3.4. As can be clearly observed, different concentrations of chlorotrimethylsilane in the range of 1.5 – 4.5 equivalents did not influence the reaction rate consistent with zero order dependence.

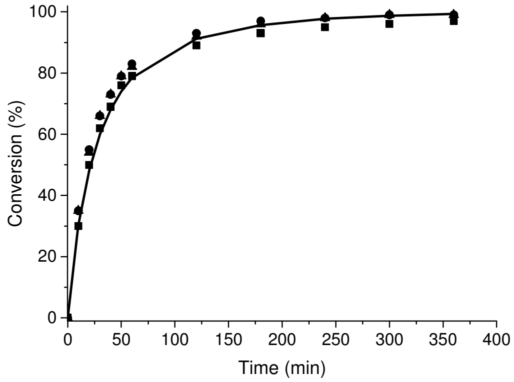
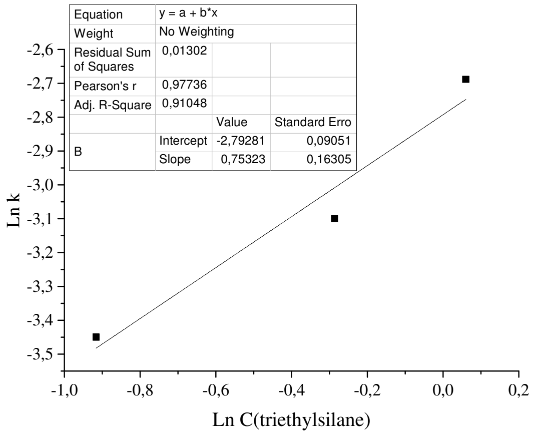


Figure 3.4. Conversion against time using 1.5 - 4.5 equivalents of chlorotrimethyl silane 4 mol-% of Fe(III) oxo acetate and 1.2 equivalents of triethylsilane. Experimental data marked as dots and model as a line.



Equation	y = a + b*x		
Weight	No Weighting		
Residual Sum of Squares	0,01302		
Pearson's r	0,97736		
Adj. R-Square	0,91048		
		Value	Standard Erro
B	Intercept	-2,79281	0,09051
	Slope	0,75323	0,16305

Figure 3.5. Ln *k* against ln *C*(triethylsilane) indicating a first order reaction with respect to triethylsilane.

Analysis of the apparent reaction rate constant with respect to concentration of triethylsilane (Figure 3.5) confirms that the reaction order with respect to this reactant is close to one.

Considering the zero order with respect to the concentration of chlorotrimethylsilane and the first order in triethylsilane, the kinetic equation corresponding to the mechanism in Scheme 3.9 can be essentially simplified and only two steps (binding of acetophenone to [FeSi] and the subsequent addition of trialkylsilane) can be considered kinetically significant. The kinetic scheme is thus reduced to a two-step sequence[29] giving the following rate expression when the first step is considered to be reversible and the second irreversible

$$r = \frac{k_1 k_2 C_{AP} C_{R_3SiH}}{k_1 C_{AP} + k_2 C_{R_3SiH} + k_{-1}} C_{cat} = \frac{\frac{k_1}{k_{-1}} k_2 C_{AP} C_{R_3SiH}}{\frac{k_1}{k_{-1}} C_{AP} + \frac{k_2}{k_{-1}} C_{R_3SiH} + 1} C_{cat} \qquad (1)$$

where C_{AP} is the concentration of acetophenone. Since the reaction order in triethylsilane is close to one eq. (1) can be further simplified by neglecting the second term in the denominator, thereby giving

$$r = \frac{k C_{AP} C_{R_3SiH}}{k' C_{AP} + 1} C_{cat} \qquad (2)$$

where $k = k_1 k_2 / k_{-1}$ and $k' = k_1 / k_{-1}$. Estimation of the kinetic parameters was carried out by nonlinear regression analysis using the simulation and parameter estimation software MODEST.[30] The ordinary differential equation (2) was solved with the backward difference method. The sum of residual squares (Q) was minimized with the hybrid Simplex-Levenberg-Marquardt method,

$$Q = \left\| y_{\exp} - y_{\text{est}} \right\|^2 = \sum_{k=1}^{\text{nsets}} \sum_{j=1}^{\text{nobs}(k)} \sum_{i=1}^{\text{nydata}(j,\,k)} (y_{\exp,\,ijk} - y_{\text{est},\,ijk})^2 \qquad (3)$$

where y_{exp} represents experimental data and y_{est} the estimated values, i.e., the concentrations.

Calculations were performed for triethylsilane (Figure 3.6 and Figure 3.7) merging all sets of experiments performed at different concentrations of the catalyst and reactants. Figure 3.6 Figure 3.7, besides the experimental data, contain also the modelling results.

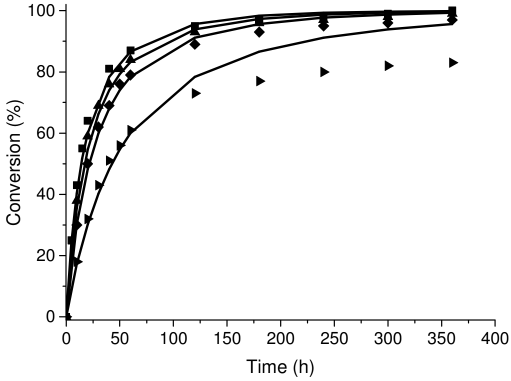


Figure 3.6. Conversion of acetophenone (2 mmol) in ethyl acetate (5 ml), with chloro trimethylsilane (3 mmol) and triethylsilane (2.4 mmol) against time using different concentrations of Fe(III) oxo acetate(2 mol-%: ▶; 4 mol-%: ◆; 5 mol-%: ▲; 6 mol-%: ■). Respective model marked as line.

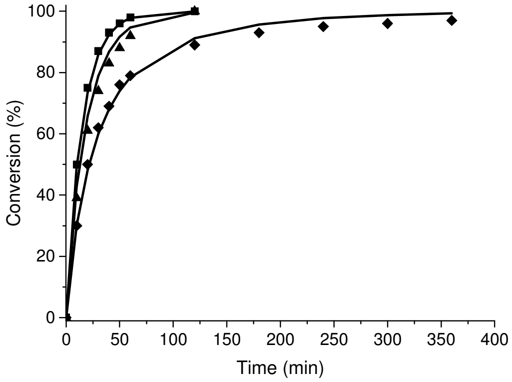


Figure 3.7. Conversion of acetophenone (2 mmol) in ethyl acetate (5 ml) against time using 4.0 mol-% of Fe(III) oxo acetate, 3 mmol of chloro trimethylsilane and various amounts of triethylsilane (1.2 eq: ◆; 2.4 eq: ▲; 3.6 eq ■). Respective model marked as line.

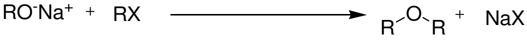
The overall fit of the final model to the experimental data can be represented with the R^2 value, which is 97.64 %, demonstrating an adequate description of the kinetic data with a model (eq. 1). The values for the rate constants are k = 10.1 $l^2/(mol^2*min)$ and k' = 0.76 l/mol, while the standard errors are 20.3% and 4.8% respectively confirming good identifiability of the parameters.

It can be concluded that the data gained from kinetic modeling of the reductive halogenation reaction is in good agreement with the experimental data and observations. While a detailed study into transitions states was not carried out, the general hypothesis for the proposed catalytic cycle was, however, supported.

3.3. Iron Catalyzed Reductive Etherification of Ketones and Aldehydes[V]

3.3.1. Introduction

The formation of carbon-oxygen bonds belongs to the oldest known transformations in synthetic organic chemistry with the first published methods dating back to 1850.[31] The method published in 1850, illustrated in Scheme 3.10, is called the "Williamson ether synthesis" according to the author. In this method, an alkoxide is used to attack an alkyl halide to form the ether. While still being one of the most widely utilized methods for synthesis of ethers, the Williamson method lacks in generality being mainly applicable for primary halides. With secondary halides, elimination and isomerization reactions of the starting material start to compete with the desired etherification, leading to a mixture of products. Few years later, Wurtz developed the synthesis of dimethyl ether from methyl iodide with the use of silver oxide.[32]

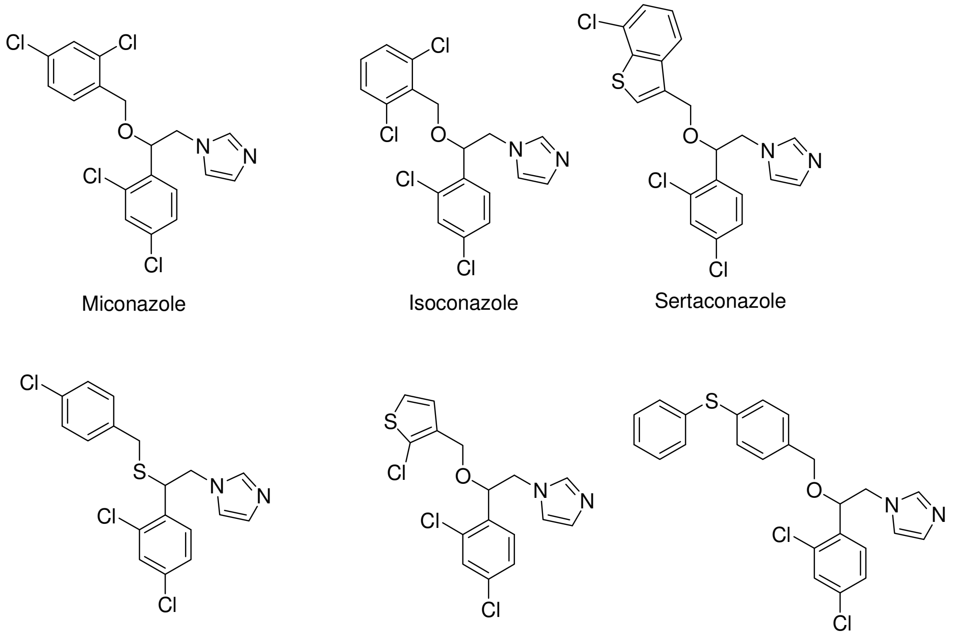


Scheme 3.10. Williamson ether synthesis.

In the 1970s, Doyle and coworkers described, in a series of papers, acid catalyzed etherifications of aldehydes in the presence of silanes.[33] The reported method suffers, however, from the need for large excess of the silane and acids required, e.g., concentrated sulphuric acid or trifluoroacetic acid. Later, Noyori reported the use of trimethylsilyl triflate as a catalyst for synthesis of ethers from acetals and ketones with trialkyl silanes as the reducing agents.[34] Subsequently, Mukaiyama and coworkers reported the use of trityl perchlorate as a catalyst for similar reactions.[35] These new methods circumvented the earlier problems, at least to some degree, providing acceptable to good yields of the isolated ethers. The application of trimethylsilyl triflate as the catalyst for ether synthesis was further improved by Olah and coworkers, extended also to the use of trimethylsilyl iodide as a separate catalyst.[36]

During the past decades several other methods using silanes as reagents and/or catalysts in the synthesis of ethers have been published. Examples of the employed catalysts include $BF_3 \cdot OEt_2$,[37] trimethylsilyl triflate or iodide,[38] $BiCl_3$ or $BiBr_3$,[39] $InBr_3$,[40] triflic acid or triflic anhydride,[41] solid acids or bases,[42] molecular iodine,[43] $Cu(OTf)_2$,[44] SbI_3[45] and $Zn(OTf)_2$.[46] Recently, two iron catalyzed methods using organosilanes as the reducing agents for synthesis of ethers have been published, involving either a condensation-type reductive reaction of ketones, aldehydes or alcohols,[47] or the reduction of carbonyl moieties of esters to yield ethers.[48]

This type of methodology can be easily envisioned to have multitude of uses in synthetic organic chemistry, in the synthesis of fine chemicals, building blocks for pharmaceuticals or direct synthesis of pharmaceuticals. Representative examples of pharmaceutical targets that could be obtained by reductive etherification methodologies are illustrated in Figure 3.8.



Miconazole

Isoconazole

Sertaconazole

Sulconazole

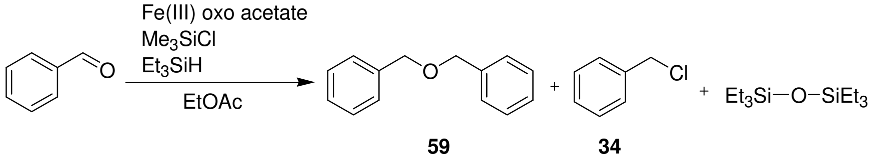
Tioconazole

Fenticonazole

Figure 3.8. Possible pharmacetutical targets for condensation type etherification from ketones and aldehydes.

3.3.2. Results and Discussion

In this work, the easily prepared iron(III) oxo acetate was investigated as a precatalyst for the synthesis of ethers from aldehydes and ketones. Additionally, chlorotrimethylsilane was used as a cocatalyst and triethylsilane as the hydride source in ethyl acetate solution, illustrated in Scheme 3.11.



59

34
Undesired
sideproduct

Scheme 3.11. Synthesis of dibenzyl ether.

Table 3.8. The influence of Fe(III) species and Me_3SiCl as catalysts on the reaction time and selectivity in the synthesis of dibenzylether.[a]

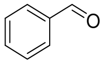
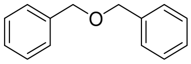
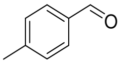
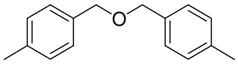
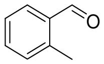
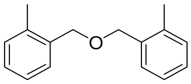
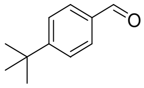
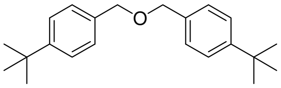
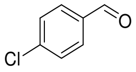
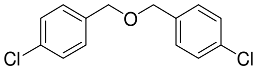
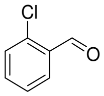
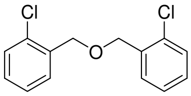
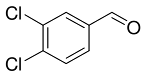
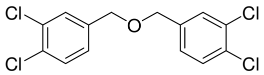
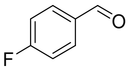
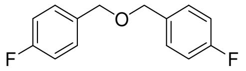
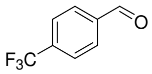
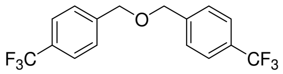
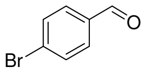
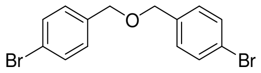
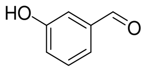
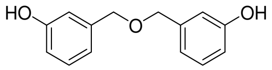
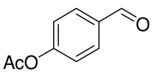
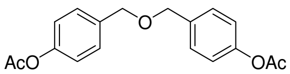
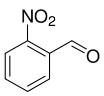
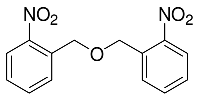
Fe(III)oxo acetate (mol-%)	Me_3SiCl (eq)	Time (h)	Selectivity **59**:**34**	Conversion[b]
4.0	1.0	1	95:5	>99
4.0	0.5	1	95:5	>99
4.0	0.25	1	95:5	>99
4.0	0.08	1	100:0	>99
4.0	0.04	24	100:0	66[c]
2.0	0.08	1	100:0	>99
2.0	0.04	6	100:0	>99
1.0	0.04	3	100:0	>99
1.0	0.02	6	100:0	51
0	0.08	-	-	0
2.0	0.00	-	-	0

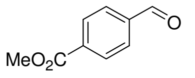
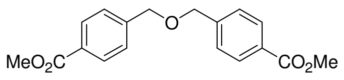
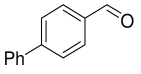
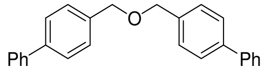
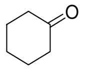
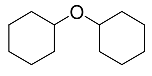
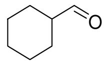
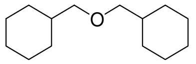
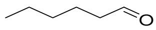
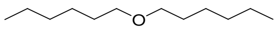
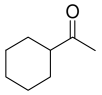
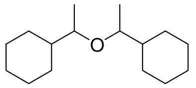
[a] Reactions carried out with 2 mmol of benzaldehyde and 2.1 mmol of triethylsilane in 1 mL of EtOAc at rt. [b] Conversion determined by GC-fid. [c] Catalyst dissolves very slowly at these conditions.

The loadings of Fe(III) oxo acetate and chlorotrimethylsilane as the catalysts were first optimized to reach satisfactory selectivities between the desired dibenzyl ether **59** and the here undesired benzyl chloride side product **34** under practical reaction times and conditions. The use of significant excess of chlorotrimethylsilane resulted in the formation of small amounts of benzyl chloride while the use of less than 0.1 equivalents of chlorotrimethylsilane prevented the formation of side product **34**. The complete data is presented in Table 3.8. The presence of both precatalysts was required in order for the reaction to proceed. In the absence of either one of these compounds, ether formation was not observed, contrary to that of previously published method in nitromethane.[47]

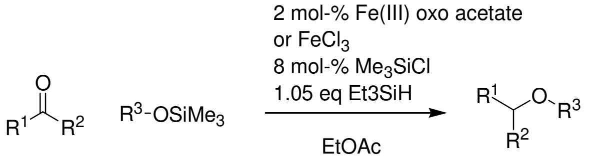
After optimization, the combination of 2.0 mol-% of Fe(III) oxo acetate with 0.08 mol-% of chlorotrimethylsilane was selected as the preferred general catalyst combination for further reaction scope screening. The initial general substrate scope investigation was conducted in 2 mmol scale by reacting benzylic aldehydes to form symmetrical ethers in short reaction times and good to excellent yields (Table 3.9.). In two cases (Table 3.9, Entries 7 and 11), the reactions were scaled up to 10 mmol scale and in one case to 100 mmol scale (Table 3.9, Entry 6). In an attempt to introduce hydroxyl substituents to the aromatic ring, *para*- and *ortho*-hydroxyl substituted benzaldehydes were investigated but while full conversion was achieved, formation of the desired ether was not observed, with only the *meta*-substituted aldehyde providing the desired product in good yield (Table 3.9, Entry 11). By use of acetyl protection, however, also the *para*-product was obtained (Table 3.9, Entry 12). Also the etherification of some non-benzylic ketones and aldehydes was briefly investigated. While no reactivity was observed with Fe(III) oxo acetate as the catalyst, good yields of the desired symmetric ethers were obtained by switching to $FeCl_3$ in combination with the chlorotrimethyl silane as a cocatalyst (Table 3.9, Entries 16-19).

Table 3.9. Investigation of substrate scope.[a]

Entry	Reagent	Time (h)		Product	Yield[b]
1		1	**59**		93
2		1	**60**		76
3		1	**61**		92
4		1	**62**		98
5		1	**63**		64
6		2	**64**		75[c]
7		2	**65**		75[d]
8		3	**66**		97
9		3	**67**		96
10		1.5	**68**		73
11		1	**69**		77
12		2	**70**		68
13		2	**71**		63[d]

14		1	**72**		79
15		1	**73**		89
16		5[e]	**75**		84
17		15 min[e]	**75**		83
18		1[e]	**76**		94
19		3[e]	**77**		64

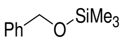
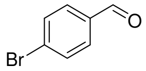
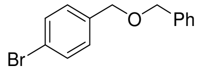
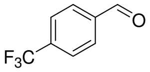
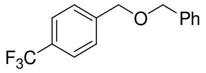
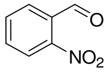
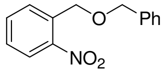
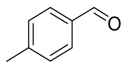
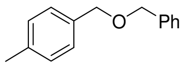
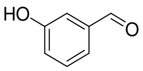
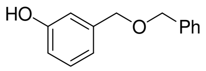
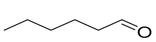
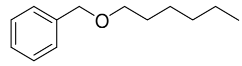
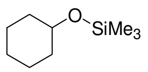
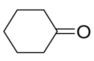
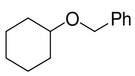
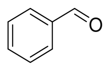
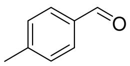
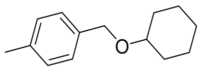
[a] General conditions: 2 mmol of the carbonyl compound, 2.1 mmol of Et_3SiH, 2.0 mol-% of Fe(III) oxo acetate and 8 mol-% of Me_3SiCl in 1 mL of EtOAc at r.t. [b] Isolated yield. [c] Reaction carried out in 100 mmol scale [d] Reaction in 10 mmol scale. [e] $FeCl_3$ used instead of Fe(III) oxo acetate.

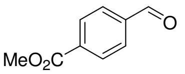
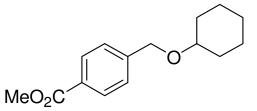
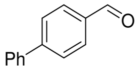
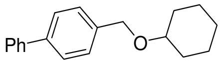
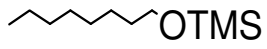
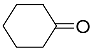
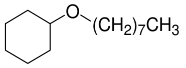
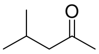
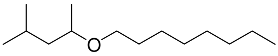
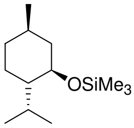
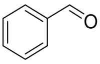
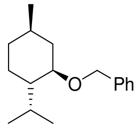
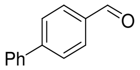
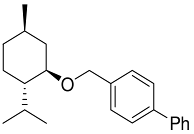
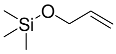
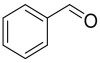
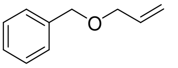
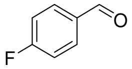
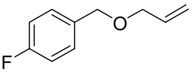
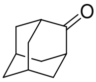
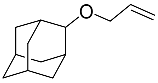


Scheme 3.12. Synthesis of unsymmetrical ethers.

The preparation of unsymmetrical ethers was then achieved using trimethylsilylated alcohols in combination with aldehyde derivatives, as illustrated in Scheme 3.12. The results are collected in Table 3.10. While good yields were observed in all reactions within one hour at room temperature, also small amounts of symmetrical ethers were produced when aliphatic ketones and aldehydes were used in combination with trimethylsilylated benzylic alcohol (Table 3.10. Entries 6 and 7). This issue could, however, be resolved by reversing the roles of the reagents (Table 3.10. Entries 8-11). The reaction of hexanal with cyclohexyl trimethylsilyl ether resulted in the formation of various side products that could not be separated from the desired product. Following the previous methodology, this was resolved by using a primary trimethylsilylated alcohol in combination with the corresponding ketone (Table 3.10, Entries 12 and 13). When trimethylsilyl derivatized (-)-menthol was reacted with benzaldehyde and biphenyl-4-carboxaldehyde, the desired ether product was formed within 30 minutes with retention of configuration at all stereocenters (Table 3.10, Entries 14 and 15).

Table 3.10. Ethers from trimethylsilylated alcohols.[a]

Entry	Reagents		Time (h)		Product	Yield (%)[b]
1			1	**78**		79
2[c]			1	**79**		89
3[c]			1	**80**		77
4			3	**81**		89
5			1	**82**		83
6			1[d]	**83**		78
7			1[d]	**84**		85
8			0.5[d]			87
9			0.5[d]	**85**		80

10			0.5^d	**86**		80
11			0.5^d	**87**		85
12			0.5^d	**88**		90
13			0.5^d	**89**		77
14			0.5^d	**90**		88
15			0.5^d	**91**		76
16			0.5^d	**92**		80
17			0.5^d	**93**		92
18			0.5^d	**94**		72

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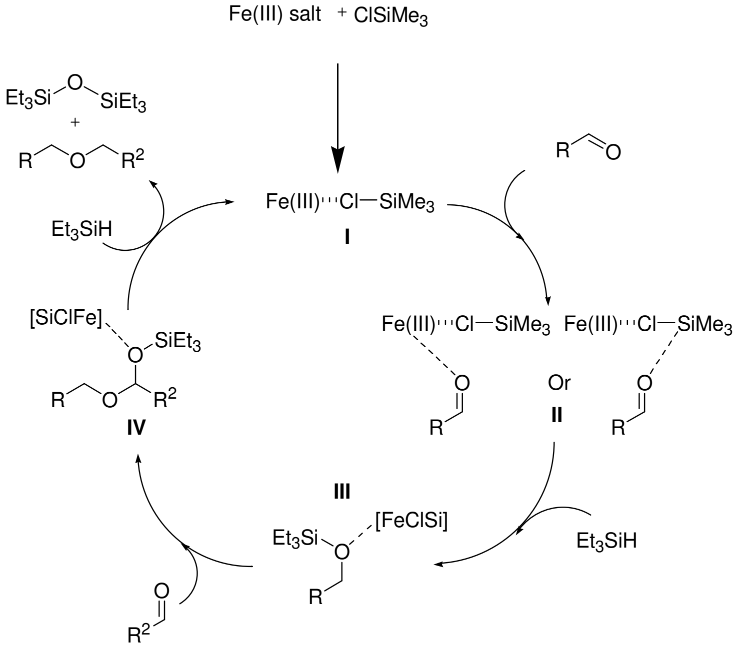
[a] General conditions: 1.0 mmol of benzyl alcohol trimethylsilyl ether, 1.0 mmol of carbonyl compound, 1.05 mmol of Et_3SiH, 2.0 mol-% Fe(III) oxo acetate and 0.08 eq. of Me_3SiCl (From 2 mmol) [b]Isolated yield. [c]Reaction done at 5 mmol scale. [d] $FeCl_3$ was used instead of Fe(III) oxo acetate

When investigating the applicability of this method to α,β-unsaturated aldehydes and ketones for preparation of symmetrical ethers it was observed that even after prolonged reaction time at room temperature only starting material could be recovered from reaction the mixture. Once again this result could be overturned by the use of pre-prepared trimethyl silylated alcohol. Thus the reaction of allyloxytrimethylsilane in combination with benzylic aldehydes produced the desired ethers in good yields (Table 3.10, Entries 16-18), although concomitant isomerization of the allylic double bond to vinylic double bond was observed to minor degree.

3.3.3. Mechanism



Scheme 3.13. Tentative catalytic cycle for the reductive etherification reaction.

Following the mechanism elucidated in Chapter 3.2.3 for reductive halogenation of acetophenone, as well as the tentative mechanism proposed by Baba and coworkers[26] (Scheme 3.8), a similar mechanistic interpretation was developed, being illustrated in Scheme 3.13. In line with the previously reported tentative reaction mechanisms and observations for similar reactions,[35,36,41c] the reaction most likely proceeds first *via* either activation of trimethylsilyl chloride or the iron(III) species in question (Scheme 3.13, **I**). This is followed by coordination of carbonyl moiety to either iron(III) or silicon species (Scheme 3.13, **II**). The formed complex undergoes hydrosilylation (Scheme 3.13, **III**), followed by subsequent S_N2 type addition to form acetal derivative (Scheme 3.13, **IV**). The formed acetal is then reduced by triethylsilane to the desired ether with siloxane formed as byproduct.

The coordination of carbonyl to silicon species (Scheme 3.13, **II**) is supported by previous reports using trimethylsilyliodide or trimethylsilyl triflate solely as the catalyst.[34,41] Consequently it can be postulated that the reaction mechanism could be a silylium ion type catalysis.[1c,49] Also the S_N2 type reaction leading to acetal derivative (Scheme 3.13, **IV**) is supported by the full retention of stereocenters when these reaction were performed using trimethylsilyl derivatised enantiopure (-)-menthol yielding products **90** and **91**.

3.4. Conclusions

A versatile synthetic methodology was developed for potential use in production of fine chemicals, pharmaceuticals and pharmaceutical intermediates. By proper choice of solvent, temperature, iron catalyst and amount of chlorotrimethylsilane, the reaction can be directed to etherification, halogenation or benzylation from benzylic carbonyl compounds under mild conditions. Almost all of the reactions proceed quickly within 1-5 hours with the yields ranging from mediocre to excellent. In cases of reductive halogenation (Chapter 3.2) and etherification (Chapter 3.3), the reactions can be carried out in economically viable solvents ethyl acetate and hexane. While the reductive benzylation (Chapter 3.1) and halogenation function with benzylic ketones and aldehydes, the reductive etherification tolerates also aliphatic ketones and aldehydes. Furthermore, by using combinations of trimethylsilyl derivatized alcohols and ketones or aldehydes, unsymmetrical ethers can be synthesized in a simple manner.

In all three reaction types limitations arise from furan derivatives and basic substrates such as organic amines. Certain substrates, such as nitro- and cyano-substituted aromatics, can also require significant optimization in order to be applicable. In all cases with aromatic substrates substituents that strongly activate the aromatic ring for electrophilic aromatic substitution resulted in poor selectivities due to side reactions. For α,β-unsaturated carbonyl compounds no reaction was observed under the conditions used. Also free carboxylic acids and amides as substituents resulted in poor conversions and selectivities due to poor solubility in ethyl acetate, dichloromethane or chloroform. A significant drawback in the reductive etherifaction (Chapter 3.3) when applied to acetophenone derivatives was that the substrates are more reactive towards the reductive halogenation. This leads to fast consumption of the chlorotrimethylsilane prior to the completion of the desired etherification reaction.

3.5. References

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4.0. Concluding Discussion

4.1. Summary and Conlusions

In this thesis work, the use of Fe(III) as a Lewis acid catalyst in the field of organosilicon chemistry under mild conditions was explored. These synthetic methodologies were steered towards fine chemical and pharmaceutical synthesis using economically viable catalysts and solvents. This thesis also included detailed computational and kinetic studies on the mechanism of chlorination of silanes. Also a short investigation on the kinetics of reductive acetophenone chlorination was carried out.

A synthetic methodology for chlorination of silanes, alkoxy silanes and silanols with the use of $FeCl_3$ as the catalyst was developed. The substrate scope was selected by considering substituents often found in organosilane compounds. Furthermore, the method was also used for monochlorination of silanes bearing two hydride moieties providing an efficient route for synthesis of racemic silanes for further modification. The reaction methodology was scaled-up to 100 mmol without significant difficulties. In order to further understand this catalytic reaction, a kinetic and computational study was carried out. The experimental and kinetic observations together with the computational insights pointed towards di or tricyclic catalytic cycle containing a separate step for catalyst deactivation. Unfortunately, the rate equation for such mechanism would require a significant amount of parameters and would be statistically unfeasible with the data collected. Consequently, the mechanism was simplified to one cycle that still could adequately explain all of the observations and also would match the collected data.

A one-pot type hydrosilylation of ketones and aldehydes with subsequent modification of the siloxy ether was investigated in Chapter 3. By use of Fe(III) catalyst in combination with organosilanes, a variety of compounds could be synthesized. When equivalent amounts of chlorotrimethyl silane and triethyl silane were used at room temperature, a reductive halogenation of benzylic carbonyl compounds was achieved. By changing the solvent to aromatic at elevated temperature, subsequent Friedel-Crafts alkylation was achieved, providing an effiecent and mild synthetic route to diarylethanes and methanes. Also the feasibility of this methodology for synthesis of triarylmethanes was investigated. Furthermore, by utilizing the chlorotrimethylsilane as a cocatalyst in combination with Fe(III) precatalyst, the reductive formation of ethers from ketones and aldehydes was observed. The reaction conditions were optimized for synthesis of symmetric and unsymmetric ethers at room temperature within a few hours. In contrast to the reductive halogenation and reductive benzylation, the reductive etherification tolerates aliphatic ketones and aldehydes as substrates.

4.2. Future Perspectives

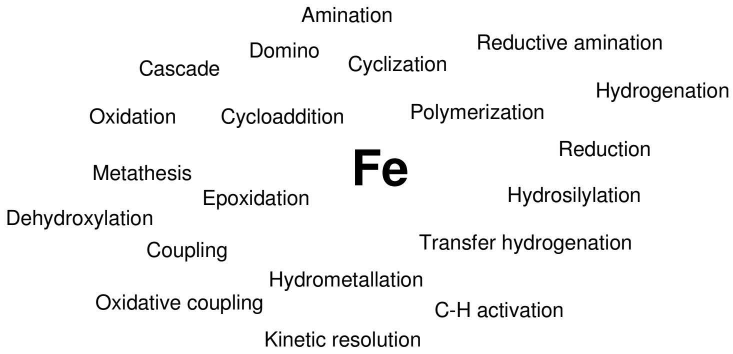

Figure 4.1. Iron in the catalysis field

As the economic feasibility of iron keeps increasing compared to that of other noble transition metals, such as palladium, platinum and gold, it is likely that the field of iron catalysis keeps growing significantly in the coming years. While it is unlikely that iron could be applied in every single catalytic transformation in organic chemistry, it has already proven to be a very versatile catalyst for a multitude of reactions, summarized in Figure 4.1. Often the methods published so far utilize benzylic compounds for the desired transformations with the aliphatic tending to be far less reactive. A number of studies with new methods are however tackling also this issue. A new wave of investigations is emerging using heterogenous iron catalysts for various transformations, such as oxidation, hydrogenation and reductive amination.

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