The Synthesis of *N*-Substituted Ferrocenes and C–H Activation Towards the Synthesis of Organosilanols

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Dissertation

The Synthesis of *N*-Substituted Ferrocenes and C–H Activation Towards the Synthesis of Organosilanols

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der Rheinisch-Westfälischen Technischen Hochschule Aachen zur Erlangung des akademischen Grades eines Doktors der Naturwissenschaften genehmigte Dissertation

vorgelegt von

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For everybody

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Parts of this work have already been published or submitted:

'*Organosilanols as Catalysts in Asymmetric Aryl Transfer Reactions*' Özçubukçu, S.; Schmidt, F.; Bolm, C. *Org. Lett.* **2005**, *7*, 1407. (This article has been highlighted in Synfact **2005**, *0*, 41.)

'*A General and Efficient Synthesis of Nitrogen-Substituted Ferrocenes*' Özçubukçu, S.; Scmitt, E.; Leifert, A.; Bolm, C.; *Synthesis* **2007**, 389.

'*Diastereoselective Catalytic C–H Activation of Ferrocenes*' Özçubukçu, S.; Bolm, C.; *Manuscript in Prep.*

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Chapter 1

Introduction

Since the first milestone in organic chemistry was established by Woehler [1] in 1828 with the synthesis of urea from various cyanates and ammonium salts, there has been an explosive proliferation of synthetic methods by which to make organic molecules that indicates their importance and application in today's world. This is perhaps best reflected in the fact that over the last 30 years, there has been an exponential increase in the number of compounds which is registered by the Chemical Abstract Service (CAS). Whereas in 1965, there was a total of only 212.000 compounds registered, by 1996, there were 15.8 million compounds listed. Currently, new compounds are registered by CAS at a rate of around 1 million per year or, in other words, at a rate of approximately 2 compounds per minute. [2] The unprecedented rate of discovery of new compounds is a consequence of new synthetic approaches to novel organic molecules being continually sought and developed.

In the pharmaceutical industry, there is a siginificant demand for one particular group of compounds, namely chiral organic molecules, and the development of more efficient synthetic methods by which to produce them. Although chiral organic molecules have long been known, the pharmaceutical implications of racemic drugs have, however, only been extensively recognized in the last 20 years, [3,4] since each enantiomer of a drug may have similar or different pharmacokinetic responses. [5,6] For example, it has been known for many years that opiate [7] enantiomers can interact with different receptors, leading to different effects in the metabolism. [8] Indeed, the (–)-enantiomers of opiates are potent narcotic analgesics, whereas their (+)-enantiomers are useful anti-tussive agent. Beside the fact that two enantiomers may have different pharmacological properties, some enantiomers have equipotent properties (*e.g.* flecainide [9]) or one enantiomer may possess all or most of the activity (*e.g.* β-blockers [10]). In the latter case, there

are some advantages to using the single enantiomer, since this exposes the patient to a lower body load and thus minimizes unwanted drug interactions. Pharmacodynamic side and drug co-administration effects can also be easily assessed if a single enantiomer is used and, likewise, enantiomer-enantiomer drug interactions and bio-inversion can be avoided. Such awareness of the influence of the chirality upon biological activity has led to an increase in the use of single enantiomers in the drug market. [11] As a result of this trend, in 1994, eight of the top ten chiral drugs were marketed as single enantiomers [12] and according to a 2005 ranking by IMS Health based on US Sales, six of the ten top selling prescription drugs are sold in the form of single enantiomers.[1]

To overcome the increased demand for chiral molecules and/or single enantiomers, intensive research is being carried out in both the academic and industrial realms. Meanwhile, recent developments like the advent of green chemistry and high raw material prices increasingly demand atom economy. The concept of atom economy was first enunciated by Trost [14, 15] at the beginning of 1990s and describes the efficiency of a chemical process in terms of all of the atoms involved. In a 100% atom economic reaction the amount of all starting materials and/or reagents equals the amount of the desired products formed: that is, no atom is wasted. One of the nicest examples to illustrate the importance of atom economy in industry is the production of ibuprofen.

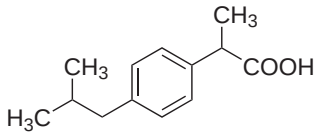

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Figure 1.1: Ibuprofen

Ibuprofen (**1**) is the active ingredient of one of the world's top selling drugs commercialized as an analgesics under varios brand names (*i.e.* Act-3, Advil, Brufen, Motrin, Nuprin, Nurofen), but which is also effective as a non steroidal anti-inflammatory drug (Figure 1.1). The current world production of ibuprofen (**1**) exceeds 15 million kilograms per year. The first synthesis of ibuprofen (**1**), patented by Alliance Boots,[2] and which has been used for the preparation for many years, had an atom economy of 40% over 6 steps. After this patent expired, other

[1] For e review about the importance of chirality in drugs, see: [13]

[2] U.S. Patent 3,385,886 Boots Pure Drug Co. Ltd. May 28, 1968.

companies started to produce ibuprofen and a three-step synthesis with an atom economy of 77% was developed. Considering the annual, global production of ibuprofen, this increase in atom economy is very dramatic and an industrial success.

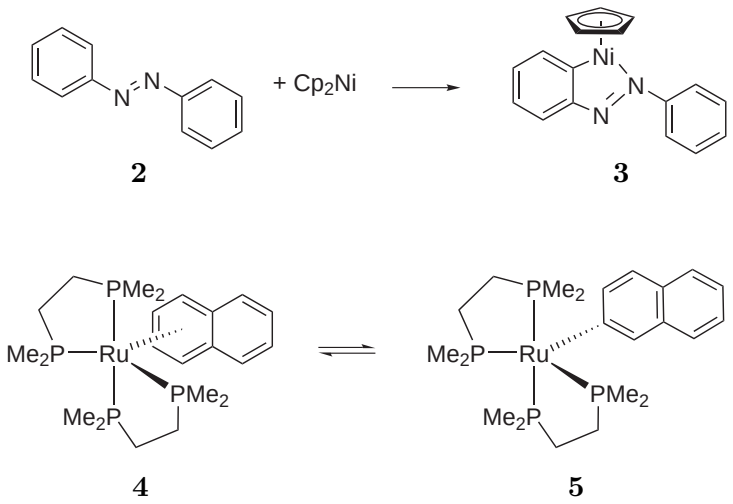
The Diels-Alder, hydrogenation, cycloaddition and C–H activation reactions are several examples of transformation having high atom economy. Click chemistry which is a novel concept [16] introduced by Sharpless, also, by the virtue of its definition requires high atom economy. Condensation reactions, in which small molecules like water, hydrogen or CO_2 are formed, also rank considerably high in terms of atom economy. In contrast, however, conventional substitution reactions exhibit poor atom economy, not only due to their tendency to generate large amounts of waste (*e.g.* in the form of salts from leaving group), but also because additional steps are often required to synthesize substrates bearing an appropriate leaving group. As a result, the direct activation of (normally unreactive) C–H bonds has found increasing favour as an alternative to conventional substitution reactions because it dispenses with the need of pre-functionalization and has a high atom economy.

1.1 C–H Activation Reactions

1.1.1 Stoichiometric C–H Activation Reactions

The development of methods for the functionalization of C–H bonds is currently one of the most attractive research subjects in the fields of organic and organometallic chemistry. [17] C–H activation reaction include the cleavage of a carbon-hydrogen bond and subsequent functionalization of carbon atom with useful chemical groups. A variety of metal complexes, consisting of a metal (M) and its associated ligands, are capable to react with a C–H bond *via* metal insertion to give an intermediate that has C–M bond which can undergo reductive elimination of metal to afford functionalized product.

Although bond dissociation energy of C–H is usually quite large, *e.g.* 105 kcal/mol for H–CH_3, and 110 kcal/mol for H–C_6H_5, [18] transition metal complexes are able to break unactivated C–H bonds. Pioneering research in C–H activation was initiated in 1963 by Kleiman and Dubeck, [19] who reported that the Cp_2Ni complex can cleave the *ortho*-C–H bond of azobenzene **2**, thereby forming an *ortho*-nickelated complex **3** (Scheme 1.1).



2 **3**

4 **5**

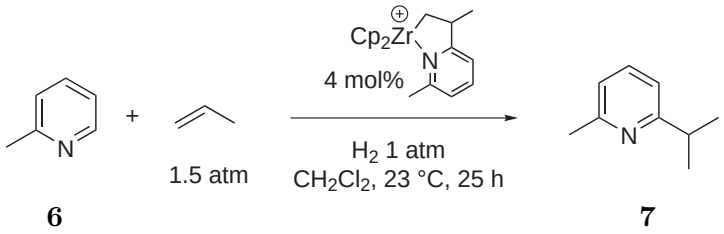
Scheme 1.1: Pioneer studies in C–H activation

Two years later, Chatt and Davidson reported [20] that the first oxidative addition of naphthalene to Ru(0) afforded complex **4**, which is in equilibrium with the π-coordinated napthalene ruthenium complex **5** (Scheme 1.1).

Subsequent to these pioneering studies, many other groups [21] have also extensively studied C–H activation reactions but almost all of them involved C–H cleavage by the stoichiometric amounts of transition metal complexes. [22] [23] The development of a catalytic version has progressed only very slow and, in many cases the use of an excess of one of the reactants and/or photo-irradiation is required to attain a reasonable catalyst turnover.

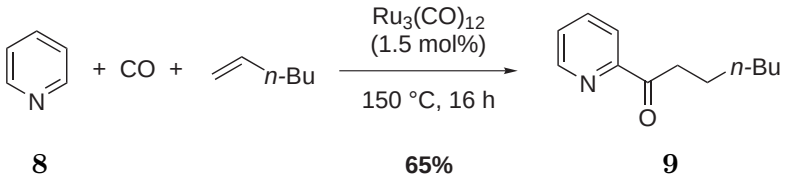
1.1.2 Pioneer Studies on Catalytic C–H Activation Reactions

Notable developments of catalytic C–H activation reactions were made as recently as the late 1980s. In 1989, Jordan reported [24] a Zr-catalyzed coupling of propene and α-picoline (**6**) which involves sequential aryl C–H activation to afford 6-Me,2-*i*-Pr-pyridine (**7**). The reaction proceeds under 1 atm of H_2, at 150 °C and conversion of α-picoline (**6**) to compound **7** was complete after 25 h. Although it is very selective and efficient, a drawback of this reaction is that hydrogenation of propene and the formation of unreactive Zr-pyridine species occur as side reactions (Scheme 1.2).



Scheme 1.2: Zr-catalyzed functionalization of α-picoline (**6**) *via* C–H activation.

In 1992, Moore published, the catalytic acylation of pyridine using CO and an olefin, employing $Ru_3(CO)_{12}$ as the catalyst. [25] This process requires harsh reaction conditions over a long reaction time (16 h) including high temperature (150 °C), and high pressure of CO (150 psi). Without CO, the acylation product cannot be observed using either thermal (180 °C) or photochemical initiation. The regioselectivities of the reactions are relatively high, but moderate conversions and turnover frequencies are obtained. In a typical reaction, pyridine (**8**) is employed as solvent and the reaction is conducted at 150 °C under 150 psi of carbon monoxide, and 1-hexene is converted to pyridyl ketone **9** with a yield of 65% after 16 h (Scheme 1.3).



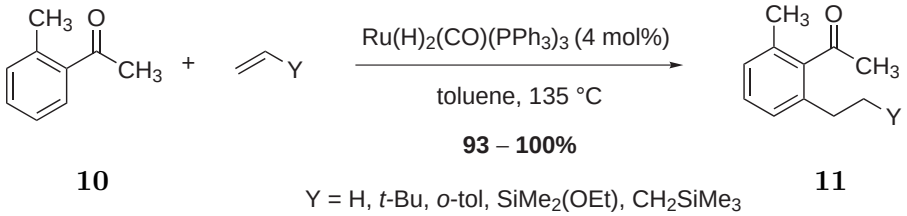
Scheme 1.3: Ru-catalyzed acylation of pyridine with CO and 1-hexene

1.1.3 Murai's Catalytic C–H Activation

Murai has intensively contributed on C–H activation reactions after his breakthrough study [26] which was a very efficient and selective *ortho*-substitution of an aromatic ketone **10** with olefins *via* C–H activation in the presence of a ruthenium catalyst, forming new C–C bond to afford product **11** (Scheme 1.4).[3] The high regioselectivity of this process is considered to be a result of the ketone functionality acting as directing group towards *ortho*-C–H activation through its ability to coordinate the ruthenium catalyst and bring the metal centre into close proximity to the *ortho*-C–H bond. In subsequent reports of Murai, many other functional groups,

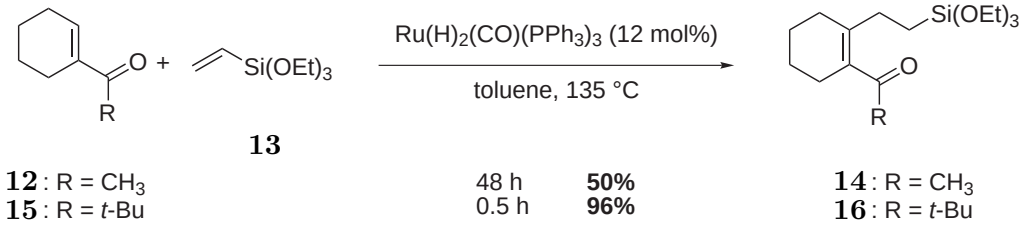
[3]For a review about the contributions of Murai and Kakiuchi on C–H activation, see: [27]

such as esters, [28] aldehydes, [29] aldimines, [30] amidinates, [31] hydrazones, [32] nitriles, [33] oxazolines, [34] amines, [35] pyrazoles [35] and pyridines [35] were used as directing groups.[4]



Scheme 1.4: Murai's Ru-catalyzed *ortho*-functionalization of an aromatic ketone *via* C–H activation with different olefins.

In addition to aromatic C–H bonds, olefinic C–H bonds can also be activated towards C–C bond formation with the aid of an appropriate catalysts. A useful example is that of the reaction between the olefinic ketone **12** and **15**, and the vinyl silane **13** which, under ruthenium-catalyzed conditions, afforded the substituted cyclohexene **14** and **16**, respectively. [37] Interestingly, the more bulky ketone **15** reacted much faster and product **16** was obtained in almost quantitative yield, compared with its less sterically-hindered counterpart (Scheme 1.5). [5,6]



Scheme 1.5: Ru-catalyzed activation of olefinic C–H bonds with olefin **13**.

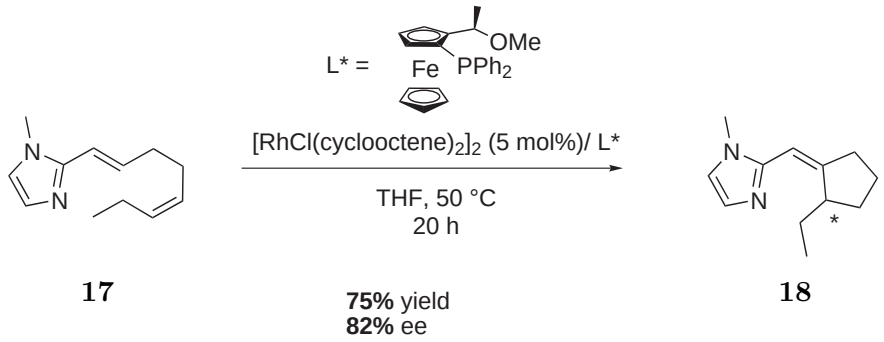
The intramolecular addition of vinylic C–H bonds to olefins was reported by Murai [40] to give 5-membered carbocycles when catalyzed by ruthenium or rhodium complexes. An asymmetric version of this reaction has been also performed by the same group, [41] in which a mono-dentate chiral ferrocenyl phophine ligand and a rhodium complex were employed as a catalyst. In the

[4]Woodgate has utilized the ruthenium catalyzed reaction of aromatic ketones with olefin for the synthesis of natural products. [36]

[5]Trost has also reported very similar results with esters (instead of ketones) by using the same catalytic system. [38]

[6]Alkylation of 2-*iso*-propenylpyridine with 1-hexene *via* Rh catalyzed olefinic C–H activation has been done by Kim [39]

reaction of imidazolyl diene **17**, at 50 °C, the product **18** is obtained in 75% yield with 82% ee (Scheme 1.6).

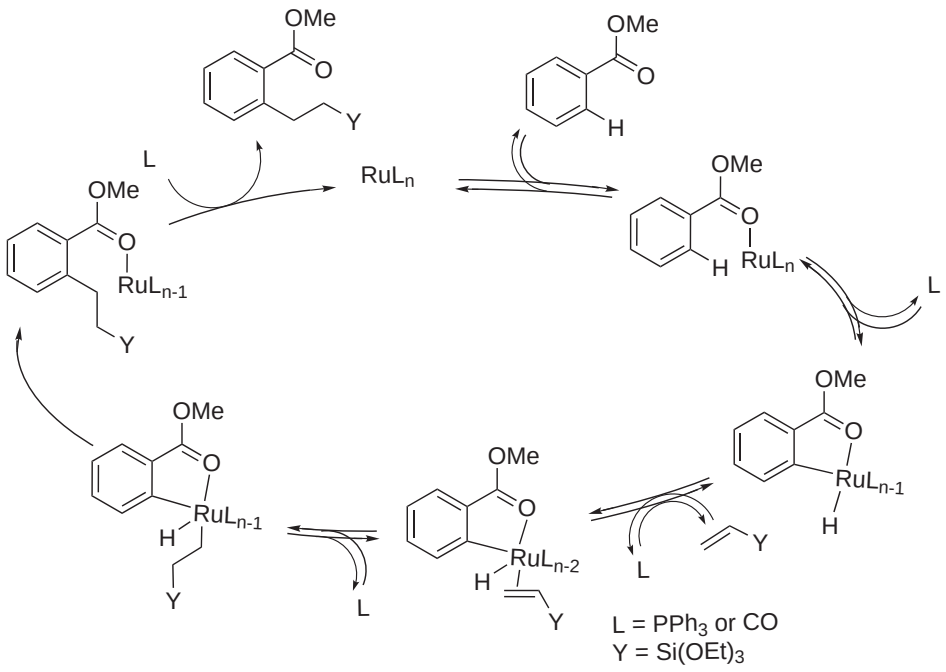


Scheme 1.6: Rh-catalyzed asymmetric intramolecular C–H activation with chiral phosphine ligand.

Mechanistic studies of Murai's olefin insertion to C–H bond

Preliminary studies into the mechanism of ruthenium catalyzed olefin insertion to C–H bond have been performed by Murai [42, 43] and several other groups [44, 45]. According to these results, the most reactive pre-catalyst was $Ru(H)_2(CO)(PPh_3)_3$, whereas $Ru(CO)_2(PPh_3)_3$, $Ru(H)_2(PPh_3)_4$, $Ru(CO)_3(PPh_3)_2$ were modestly effective with decreasing activity in this order, and $Ru_3(CO)_{12}$ was not active. This suggests that neither H nor CO is the necessary ligand and according to NMR studies, [43] it is believed that the when pre-catalyst $Ru(H)_2(CO)(PPh_3)_3$ is used, hydrogenation of olefin occurs to give a zerovalent ruthenium species such as $Ru(CO)(PPh_3)_3$ which is thought to be the active catalyst.

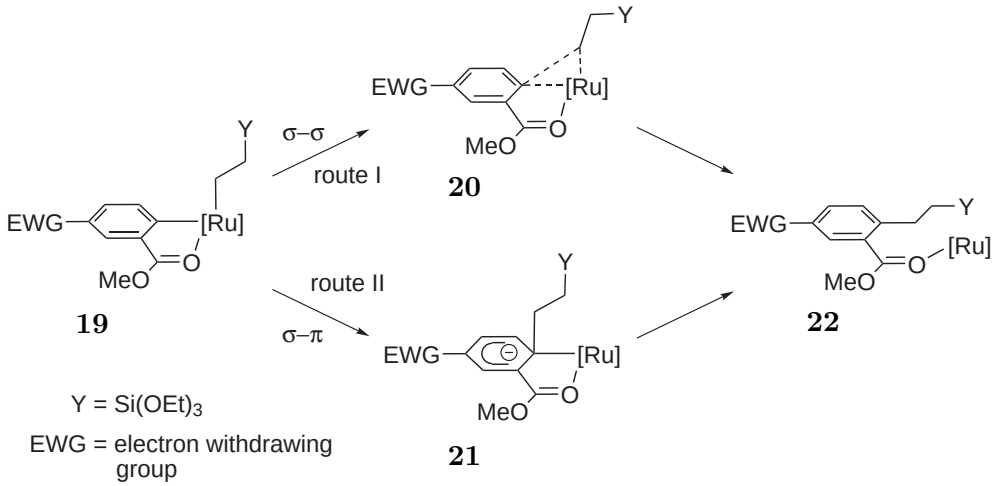
Since the C–H bond energy is quite high, it is easy to speculate that the rate-determining step involves C–H cleavage but deuterium labeling experiments shows that this assumption is not correct. When a non-reactive deuterated substrate (methyl benzoate) was treated under Murai's conditions (shown in Scheme 1.4), as expected, no conversion was observed as shown by GC study. However, ^{1}H NMR experiment showed that complete H/D scrambling of the two *ortho* and three olefinic protons occured. This studies proves the existence of a pre-equilibrium process prior to the reductive elimination step which indicates that the C–H bond cleavage step is quite facial and that the reductive elimination step of the catalytic cycle is, in fact, the rate-determining step. [46]



Scheme 1.7: Murai's proposed mechanism for Ru-catalyzed C–H activation.

Based on these preliminary experimental studies, Murai proposed the reaction mechanism shown in Scheme 1.7.

Murai also claimed that although the reductive elimination of ruthenium and the C-C bond formation steps, shown in Scheme 1.7, can occur in a sequential fashion (route I), it is also possible that they may also occur *via* a not yet fully-understood mechanism in which both processes occur simultaneously (route II), as described in Scheme 1.8. [43].

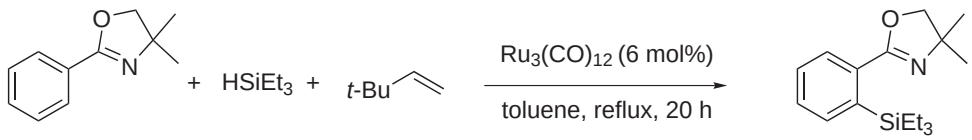


Scheme 1.8: Two plausible mechanism for the reductive elimination step of the proposed catalytic cycle.

According to the results that suggest that reductive elimination step to be the rate-determining step, an electron withdrawing group on the aromatic ring would be expected to retard the rate of the reductive elimination process. However, when aromatic esters that are substituted with an electron withdrawing group are reacted with an olefin, reductive elimination of intermediate **19** to form intermediate **22** is apparently facilitated [47]. Based on these observations, Murai proposed that a migration mechanism for the reductive elimination is favored compared to the usual σ-σ coupling mechanism through the formation of intermediate **20**. In the case of σ-π, the shift of the alkyl group from ruthenium to the aromatic ring generates a negative charge which is stabilized by the electron withdrawing group (intermediate **21**, Scheme 1.8). This mechanism is consistent with the observation which suggest that *meta*-oriented electron withdrawing groups accelerate the reaction better than the *ortho*- or *para*-ones.

Murai's Catalytic Insertion of Silicon to into the C–H Bond

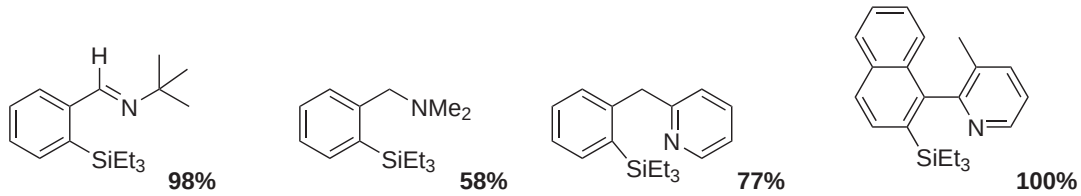
Murai has also reported [34] ruthenium catalyzed dehydrogenative silylation of aromatic C–H bonds with triethylsilane, using an olefin (*tert*-butylethylene or norbornene) which acts as a hydrogen scavenger and effects the reaction in a catalytic manner. The oxazoline moiety acts as an *ortho*-directing group to exclusively furnish the *ortho*-product in high yields when using excess amounts of silane and olefin. For example, silylation of oxazoline **23** affords product **24** in 93% yield after reflux in toluene for 20 h (Scheme 1.9). Beside the excessive amounts of reagent needed to effect the reaction, another limitation of this reaction is that it requires the use of triethylsilane because other types of silane such as triethoxysilane, triisopropyl silane, ethoxydimethyl silane or *tert*-butyldimethylsilane, fail to react sufficiently under the reaction conditions.



23 **24**

Scheme 1.9: Ru-catalyzed silylation of the *ortho* C–H bond of phenyl oxazoline **23**.

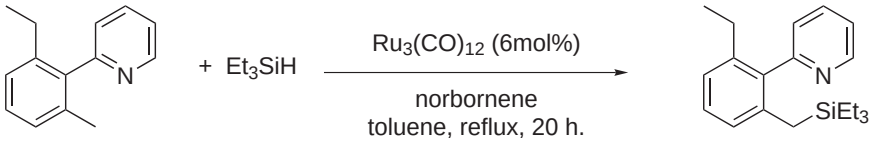
The use of different directing groups other than oxazoline also furnishes the corresponding *ortho*-silylated arenes **25**–**28** in good to excellent yields (Figure 1.2). [35]



25 **26** **27** **28**

Figure 1.2: Products formed using various directing groups to effect Ru-catalyzed *ortho*-silylation.

Recently, Kakiuchi has extended this method to the activation of sp^3-hybridized C–H bond. [48] Concretely, the silylation of benzylic C–H bonds of arylpyridines can be successfully performed by employing $Ru_3(CO)_{12}$ as catalyst and norbornene as hydrogen scavenger. This reaction is selective for *ortho*-CH_3 groups rather than *ortho*-CH_2 groups. For example, the primary carbon at the benzylic position in the arylpyridine **29** is selectively silylated and affords the product **30** in 53% yield after reflux in toluene for 20 h (Scheme 1.10).



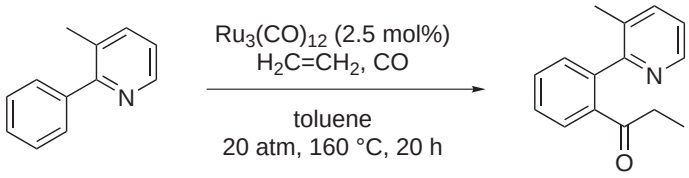
29 **53%** **30**

Scheme 1.10: Silylation of a benzylic C–H bond of arylpryidine **29** *via* Ru-catalyzed C–H activation.

Murai's carbonylation at a C–H Bond on aromatic ring

Murai has also reported the first effective ruthenium catalyzed carbonylation at a C–H bond in a benzene ring, [49] effected in a similar fashion to the olefin insertion to C–H bond, in that a directing group located at an appropriate position on the aromatic ring was employed to ensure that catalytic cleavage of the *ortho*-oriented C–H bond was performed with high regioselectivity and efficiency. For instance, the reaction of 3-methly-2-phenyl-pyridine (**31**) with ethylene and CO proceeds at 160 °C, to give aromatic ketone **32** in high yield (94%) (Figure 1.11). Simple aromatic rings such as benzene, pyridine or anisole did not serve as suitable substrates towards carbonylation. Instead, the presence of an effective directing group such as pyridine or imine

moieties, were found to be required for the C–H functionalization to occur.

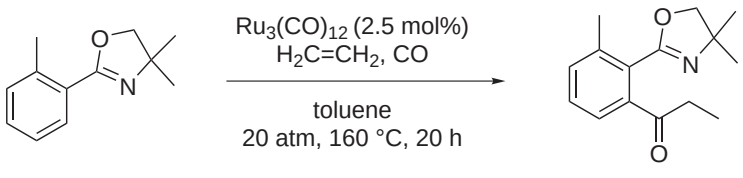


31 **94%** **32**

Scheme 1.11: Catalytic carbonylation of phenyl ring using a pyridine moiety as a directing group.

Unfortunately, however, the imine moiety is not stable under these carbonylation conditions and whereas the pyridine moiety does so, it is not so easy to remove after the desired functionalization has been performed. Furthermore, neither of these directing groups are easily transformed into other functionalities and, as such, these moieties have been superseded by the much more versatile oxazoline directing group.

Oxazolines can be easily synthesized from carboxylic acids, [50,51] aldehydes [52] or cyanides [53,54] *via* different well-established methods. Furthermore, and more importantly, they can be readily transformed into other functional groups such as carboxylic acids and esters [55] or aldehydes, [56] and also give better reactivity and site selectivity towards carbonylation of the *ortho*-C–H bond in aromatic rings. [57] Other five-membered N-heteroaromatic compounds, such as pyrazoles, oxazoles, and thiazoles, can also be used for the carbonylation reaction, giving the same selectivity. For example, Ru-catalyzed carbonylation of aryl oxazoline **33** with ethylene and carbonmonoxide proceeds at 160 °C in toluene affording the desired aromatic ketone **34** in 98% yield after 20 h (Scheme 1.12).

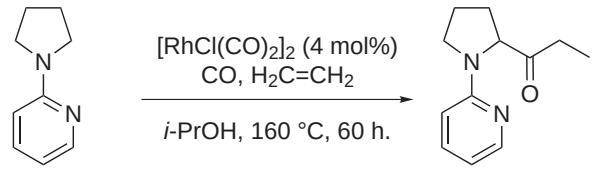


33 **98%** **34**

Scheme 1.12: Ru-catalyzed carbonylation of an aromatic ring using an oxazoline as a directing group.

Murai reported that [58] carbonylation of an sp^3 hybridized C–H bond adjacent to a nitrogen

atom can be attained by means of pyridine or phenyl ketone moieties as a directing groups. In the following example, $[RhCl(cod)]_2$ is the choice of catalyst complex and *iso*-propanol is used as solvent. It is a three-component reaction with substrate **35**, CO and ethylene. The reaction is quite selective but long reaction time and high temperature are necessary to obtain ketone **36** in high yield (Scheme 1.13).

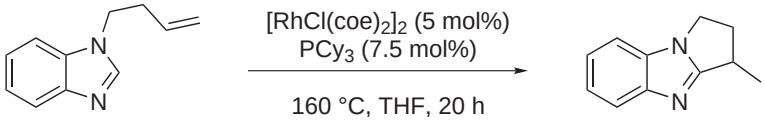


35 **70%** **36**

Scheme 1.13: Carbonylation of an sp^3-hybridized C–H bond adjacent to a nitrogen atom in alkylamines catalyzed by a rhodium complex.

1.1.4 Catalytic Olefin Insertion into the C–H Bond

In 2001, Bergman and Ellman reported an intramolecular C–H activation of a range of substrates including mono-, di- and trisubstituted alkenes catalyzed by rhodium to form various five- and six-membered heterocycles. [59] For instance, intramolecular reaction of benzimidazole derivative **37** in the presence of rhodium catalyst proceeds at 160 °C in tetrahydrofuran to give cyclized benzimidazole derivative **38** in 79% yield after 20 h (Scheme 1.14).



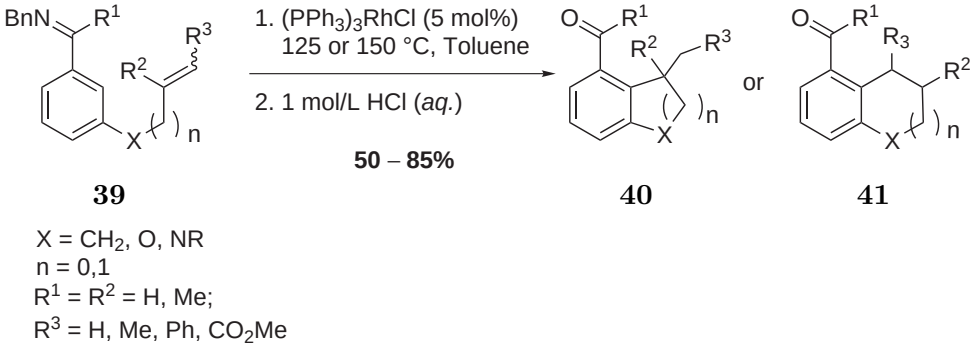
37 **79%** **38**

Scheme 1.14: Rh-catalyzed intramolecular C–H activation of benzimidazole derivative **37**.

A microwave-assisted version of this method was published some years later by Bergman and Ellman, [60] in which reactions of relatively short duration (15–20 min) were performed to obtain products in similar yield compared to conventional heating procedures.

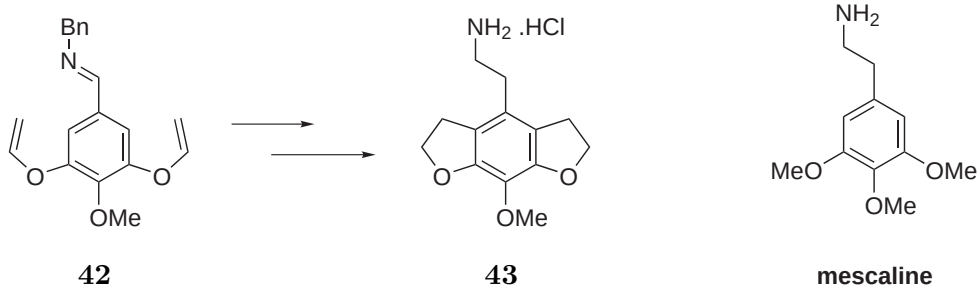
Bergman and Ellman also developed a method using Wilkinson's catalyst for the cyclization of olefins tethered to aromatic imines **39** in which the latter act as directing groups. [61,62] This

is a novel method for the synthesis of indane, tetralene, dihydrobenzofuran and dihydroindole derivatives **40-41** which may be varied by the use of different tether lengths, by incorporation of heteroatoms into the tether and by use of alkenes with various substitution patterns (Scheme 1.15). [7]



Scheme 1.15: Rh-catalyzed C–H activation of aromatic rings using an imine as a directing group.

These authors also applied this method to the synthesis of a mescaline analog. [64] Starting from a suitable vinyl ether **42**, tricyclic mescaline analog **43** could be obtained through few steps in which C–H activation reaction was the key step (Scheme 1.16).[8]

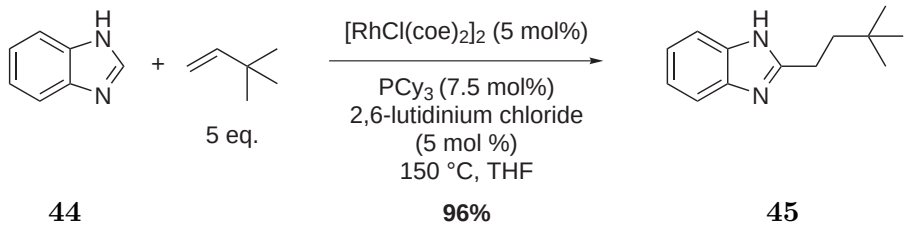


Scheme 1.16: Application of Rh-catalyzed C–H activation method in the synthesis of mescaline derivative **43**.

[7] In 2003, Bergman and Ellman reported the same reaction in an enantioselective manner by using chiral phosphoramidite ligands. [63]

[8] Recently, Sames has showed [65,66] a similar intramolecular cyclization *via* metal catalyzed C–H bond cleavage. In the presence of $PtCl_4$ as catalyst, aromatic propargyl ethers can be inserted to aromatic C–H bond, forming 6-endo products. Propargyl amines and alkynoate esters can also undergo cyclization reaction in the same fashion. Various substituents on aromatic ring are generally tolerable and heteroaromatic derivatives can also be used.

An intermolecular version of this reaction appeared one year later as the first report on an intermolecular coupling of alkenes with aromatic heterocycles. [67] Additives such as 2,6-lutidinium chloride play a significant role in increasing the yield of this reaction. As shown in Scheme 1.17, benzimidazole (**44**) and *tert*-butyl ethylene can react to give the benzimidazol derivative **45** *via* C–H activation catalyzed by Rh in the presence of 2,6-lutidinium chloride.

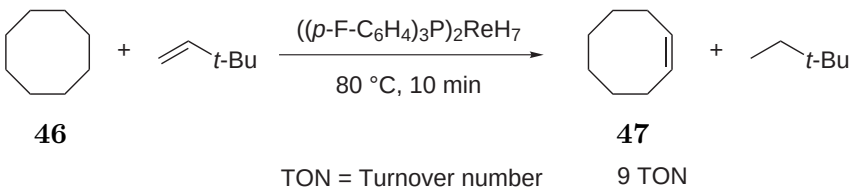


Scheme 1.17: Rh-catalyzed intermolecular alkene insertion to the C–H bond of benzimidazole (**44**).

In addition to imidazoles, insertion of olefinolefins into the C–H bond of various oxazolines is also possible using a rhodium catalyst. [68] In a similar manner, arylation of other heterocycles can be attained by using iodobenzene derivatives. [69] [9]

1.1.5 Catalytic Dehydrogenation of Alkanes

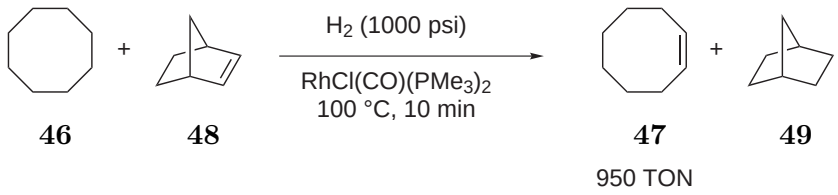
Converting a saturated carbon chain into an olefin is a highly valuable reaction since a wide variety of functional groups can be achieved by transformations of C–C double bonds. In 1979, Crabtree demonstrated that it was possible to dehydrogenate alkanes using a stoichiometric amount of an iridium phosphine complex. [71] Later, in 1983, Baudry and Ephritikhine reported [72] the first catalytic tranformation of cyclooctane (**46**) into cyclooctene (**47**) with the aid of rhenium catalyst in the presence of *tert*-butylethylene as hydrogen scavenger under thermal conditions with a turnover numbers (TON) of 9 (Scheme 1.18).



Scheme 1.18: First catalytic dehydrogenation of alkanes with rhenium as catalyst.

[9] Recently, mechanistic studies including a survey of functional group compatibility on both alkene and heterocycles have been reported. [70]

Following these pioneering studies, numerous catalyst systems for the dehydrogenation of alkanes have been examined and reported by many other research groups.[10] Of these, Goldman has developed [76] a unique and more efficient catalyst system that paradoxically, utilizes a high pressure of hydrogen for dehydrogenation. Under 1000 psi of hydrogen at 100 °C for 15 min., the rhodium complex $RhCl(CO)(PMe_3)_2$ generates cyclooctene (**47**) from cyclooctane (**46**) with a TON of 950 by using norbornene (**48**) as hydrogen scavenger to form norbornane (**49**) (Scheme 1.19).



Scheme 1.19: Dehydrogenation of alkanes with H_2.

According to the proposed mechanism by Goldman, CO is reductively eliminated from the rhodium complex and H_2 is oxidatively added to the metal to form the catalytically active species $RhCl(PMe_3)_2H_2$. Subsequently, H_2 is transfered to the hydrogen-scavenger olefin, such that the active metal center can remove H_2 from the alkane and again become ready to repeat the catalytic cycle.

In 1990, Saito found [77] that instead of using a hydrogen scavenger, high temperature reflux condition was sufficient for continuous removal of hydrogen using Wilkinson catalyst. The disadvantages of this method are that long reaction times (24 h) are required and that occurs in low turnover numbers (14 TON). [11]

1.1.6 Catalytic Borylation of C–H Bonds

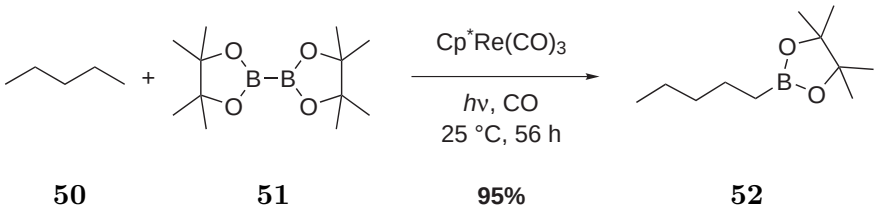
Organoborons are highly versatile compounds in organic synthesis, because they can be easily converted to other functional groups. By way of example, organoboranes have found particular application as powerful reagents in the Suzuki-Miyaura cross-coupling with organohalides. [80]

There are many methods by which to make organoboranes but particular interest has recently been focused on the use of C–H activation reactions for the direct borylation of arenes and alkanes using transition metal complexes. In 1995, Hartwig described [81] the first example of

[10] For some representative examples, see: [73–75]

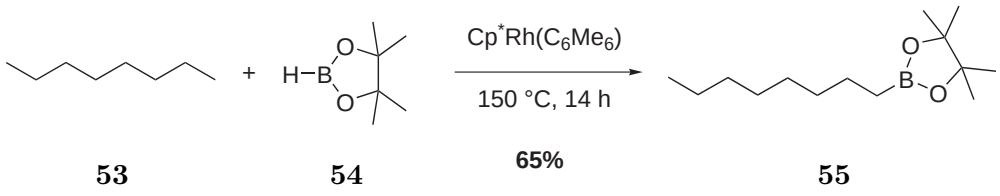
[11] This simple dehydrogenation system has been improved by Crabtree [78] and some others [79].

this transformation using a stoichiometric amount of a cyrhetrenes complex under irradiative conditions to give an aryl borane compound in high yield and selectivity. Following this method, for example, using photo-irradiation and CO atmosphere, reaction of *n*-pentane (**50**) with B_2pin_2 (**51**) regioselectively affords *n*-pentyl borane **52** (Scheme 1.20).



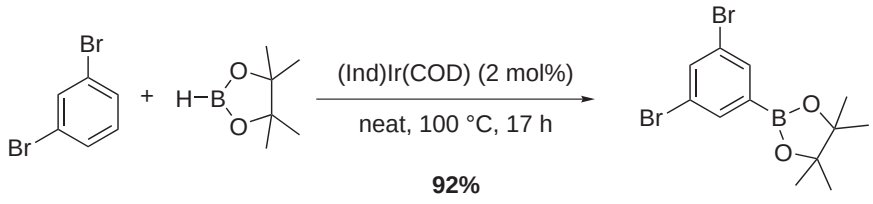
Scheme 1.20: First stoichiometric alkane borylation mediated by a rhenium complex.

Several years later, Hartwig reported [82] alkane borylation using a vanadium complex and, more recently, developed [83] the first catalytic version of a borylation using rhodium complex to achieve C–H activation in high yield and regioselectivity. A remarkable improvement to this reaction was achieved in 2000, again by Hartwig. [84] Alkane borylation could be effected using a rhodium complex as a catalyst without the necessity of photo-irradiation or a CO atmophere. For example, the reaction of *n*-octane (**53**) with pinacol borane **54** proceeds at 150 °C, to regioselectively afford *n*-octyl borane **55** in good yield (Scheme 1.21).



Scheme 1.21: Rh-catalyzed borylation of octane without photo-irradition.

Furthermore, borylation of aromatic compound is also possible under these conditions. Although, however, the borylation of mono-substituted benzenes faces some regioselective issue, [85] 1,3-disubstituted benzenes shows nice regioselectivity at the 5-position and very high yields. Five- and six-membered heteroaromatic compounds are also applicable to the borylation reaction. [85, 86] For instance, neat 1,3-dibromo benzene (**56**) reacts with pinacolborane **54**, at 100 °C, to regioselectively afford boryl arene **57** in high yield (Figure 1.22).



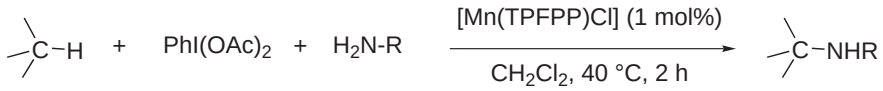
56 **54** **57**

Scheme 1.22: Ir-catalyzed borylation of 1,3-dibromobenzene (**56**) without photo-irradition.

Very recently, Smith reported the Ir-catalyzed borylation of 2-substituted indoles at the 7-position in good yields. [87]

1.1.7 Catalytic Insertion of Nitrogen into the C–H Bond

Research into the catalytic insertion of nitrogen into C–H bonds was pioneered by Breslow who reported the amination of a saturated C–H bond with a pre-formed nitrene source, namely, PhI=NR, formed from $PhI(OAc)_2$ and the corresponding primary amine **59**, in the presence of iron or manganese porphyrins. [88] Although several contributions followed this initial work, the first real breakthrough came upon appearance of a paper by Che, [89] describing the amination of saturated C–H bonds catalyzed by electron-deficient ruthenium and manganese porphyrins using a nitrogen source, that is prepared *in situ* from sulfonamides and iodosobenzene diacetate. The *in situ* formation of nitrenes is a significant improvement, even allowing the direct amination of, for example, indane with trifluoroacetamide, to occur. Typical substrates for amination are ethyl benzene, indane, adamantane, THF and cyclohexene, and can be effected using a number of amines such as tosyl and mesyl amine for *in situ* nitrene formation to afford amine products **60** (Scheme 1.23).

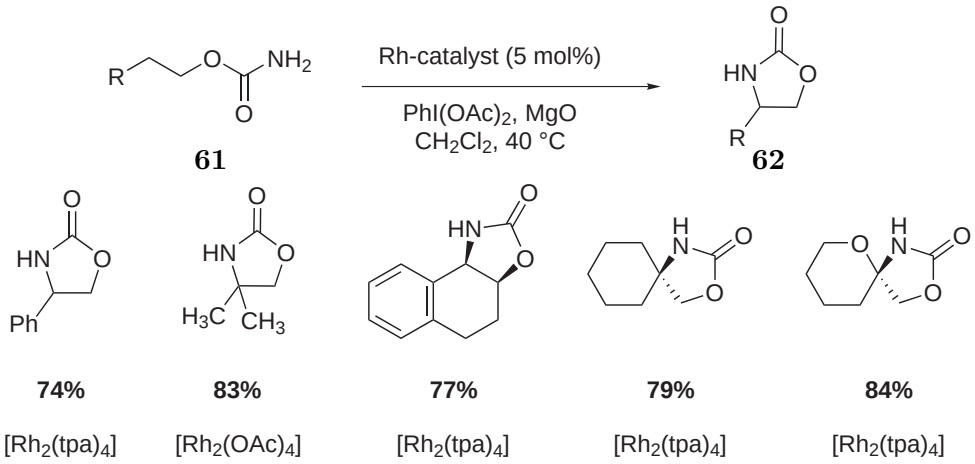


58 **59** **60**

Scheme 1.23: Mn-catalyzed C–H amination of alkanes **58** with *in situ* prepared nitrenes from $PhI(OAc)_2$ and amines **59**

In 2001, Du Bois reported [90] a further notable advance in this area. He prepared a variety

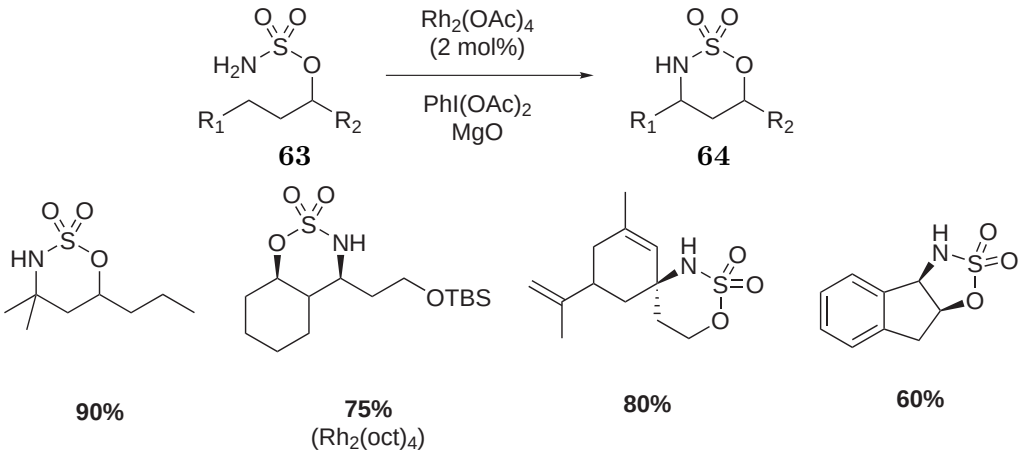
of oxazolidinones **62** from simple carbamates **61** *via* regioselective, intramolecular rhodium catalyzed C–H insertion mediated with $PhI(OAc)_2$ and a base. The latter is a necessary additive for this transformation in order to scavenge the acetic acid generated during the nitrene formation. The products obtained are precursors of 1,2-amino alcohols. Significantly, when nitrogen is inserted in the C–H bond of a chiral, enantippure substrate, only one enantiomer is formed, demonstrating that the reaction is stereospecific and occurs *via* a concerted insertion process (Scheme 1.24).



Scheme 1.24: Rh-catalyzed intramolecular amination of C–H bond of carbamates **61**.

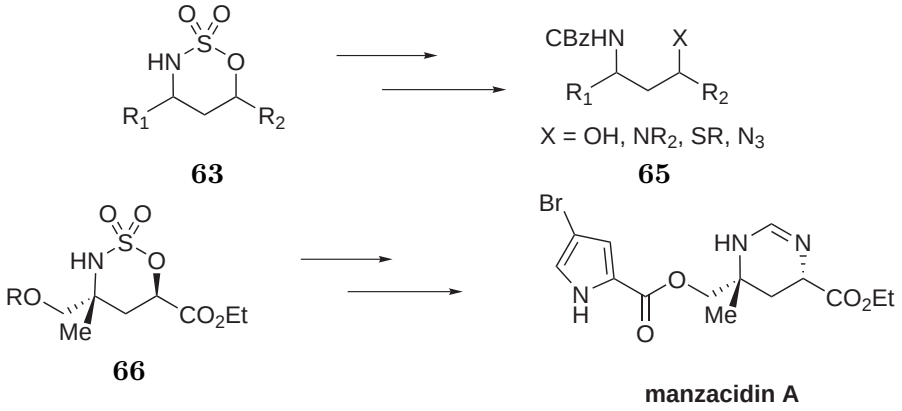
Du Bois also showed [91] sulfamate esters to be applicable in the same reaction. The main advantage conferred upon the reaction with the use of sulfamate esters is preferential formation of six-membered heterocycles. As a result, by converting the same simple alcohols into either the carbamate or the sulfamate products using the appropriate protocol, it is possible to get either the 1,2- or 1,3-amino alcohols, respectively (Scheme 1.25).[12]

[12]Cyclic sulfamate esters posessing an N,O-acetal moeity exhibit properties consistent with an iminium ion equivalent and, as such, a suitable nucleophile can be added to these molecules for further functionalization.



Scheme 1.25: Rh-catalyzed intramolecular amination of C–H bond of sulfamates **63**.

Given the facility by which a variety of 1,3-difunctionalized compounds **65** (not just amino alcohols) can be synthesized using this two-step process (of C–H insertion and opening of the sulfamate ester **63** with a nucleophile), Du Bois has utilized [92] this method in the total synthesis of manzacidin A and β-amino acids. [93] Starting from an enantiopure alcohol, a 1,3-amino alcohol moiety **66** was obtained *via* formation of the sulfamate ester through C–H insertion, and this was then converted into the natural product manzacidin A (Scheme 1.26).



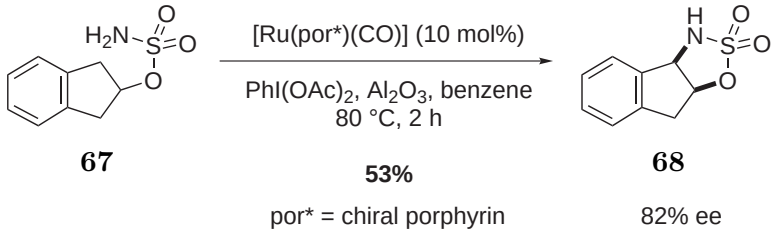
Scheme 1.26: Total synthesis of manzaicidin A *via* C–H insertion as a key step.

Other metals[13] such as silver and ruthenium can be also utilized in the intramolecular amination of C–H bonds.[14]

[13] For representative examples, see: [94, 95]

[14] Sames has also contributed on this field, through his discovery of a chelate-directed, intramolecular amination of C–H bonds catalyzed by platinium. [96]

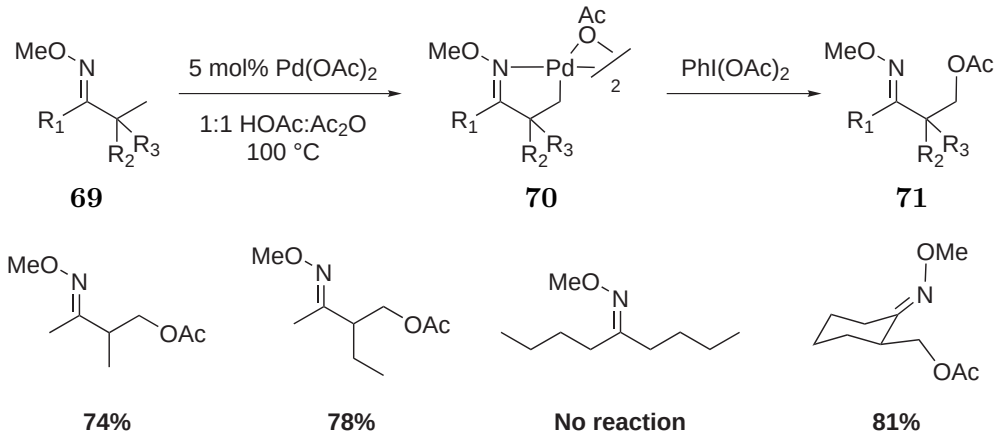
Furthermore, the enantioselective version of catalytic C–H amination was first reported by Müllet [97], as preliminary results, in which a chiral Rh-complex was utilized as catalyst, and an aminoindane derivative was obtained in 71% yield with 31% ee. Moreover, Che has contributed [98] on this topic expanding the scope of the reaction and increasing the enantiomeric excesses up to 86% with intramolecular amidation of sulfamate esters. For example, Ru-catalyzed enantioselective intramolecular C–H amidation of sulfamate ester **67**, by means of chiral porphyrin ligand, furnished the cyclic sulfamate **68** in moderate yield and good enantiomeric excess (Scheme 1.27).



Scheme 1.27: Ru-catalyzed intramolecular asymmetric C–H amidation of sulfamate **67**.

1.1.8 Catalytic Insertion of Oxygen into the C–H Bond

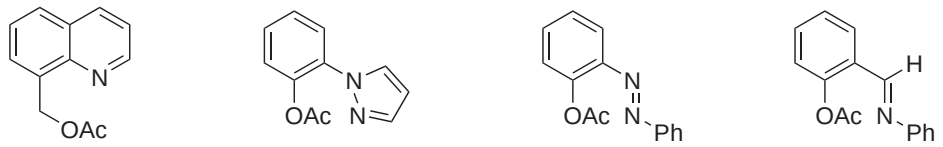
Recently, Sanford has reported [99] the Pd-catalyzed oxidation of otherwise unreactive sp^3 hybridized C–H bonds of oxime or pyridine substrates. However, this process is normally restricted to the directing group effect of the oxime and pyridine moieties results in high regio- and chemoselectivity for activation of β-C–H bonds, since more highly substituted substrates which don't have a β-CH_3 group don't give C–H activation reaction due to steric reasons.



Scheme 1.28: Sanford's Pd-catalyzed oxidation of sp^3 hydridized C–H bonds.

The product **71** obtained from oxime substrates **69**, through a palladacycle intermediate **70**, is mostly isolated as a mixture of E/Z isomers. Another drawback of this transformation is the requirement of stoichiometric amount of $PhI(OAc)_2$ as oxidant.

More recently Sanford has shown that a similar method involving the use of various directing groups including pyridine, pyrazole and azobenzene moieties is applicable to insert oxygen into the unactivated C–H bonds of aromatic rings (Figure 1.29). [100]

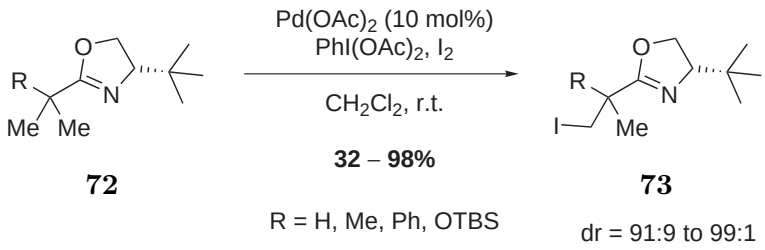


88% **54%** **62%** **47%**

Scheme 1.29: Sanford's Pd-catalyzed oxidation of sp^3 hydridized C–H bonds with different directing groups.

Pd-catalyzed, chelate-directed acetoxylation of *meta*-substituted arene substrates exhibits high regioselectivity for functionalization at the less-substituted *ortho*-position. Unlike directed *orto*-lithiation and Ru-catalyzed C–H activation reactions, substituents such as OMe, OMOM and F do not exhibit secondary directing effects. [101]

As an extension of this research, Sanford has also reported insertion of halogen atoms into C–H bonds using the same metal system. Using *N*-halosuccinamides as halogen sources in acetonitrile, it is possible to halogenate aromatic C–H bonds with the help of pyridine or oxime moieties as directing groups. More recently, Yu [102, 103] has utilized oxazolines as directing groups for the halogenation of sp^3-hybridized C–H bonds with iodine, using palladium as a catalyst in the presence of $PhI(OAc)_2$. For example, Pd-catalyzed diastereoselective iodination of oxazolines **72** furnished iodooxazoline **73** in poor to excellent yields with high diastereoselectivities, depending on R substitutent (Scheme 1.30).



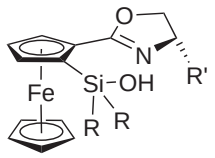
72 **73**

dr = 91:9 to 99:1

Scheme 1.30: Yu's Pd-catalyzed diastereoselective iodination of sp^3 hydridized C–H bond.

1.2 Objectives of the Research

As highlighted in the introduction part, functionalization of otherwise unreactive C–H bonds with metal catalysts is currently one of the most attractive research topics in the fields of organic and organometallic chemistry. Although the catalytic C–H activation of different aromatic compounds is well-established in literature, to the best of our knowledge, there is no report on catalytic and diastereoselective C–H tranformation of ferrocenes. Since, as it will be described in Chapter 2, we are particularly interested in ferrocenyl oxazolines **153** having silanol moeity (Figure 1.3), we aimed to synhtesize such compounds *via* C–H activation reaction, which is analog to Murai's Ru-catalyzed *ortho*-silylation of aryl oxazolines (see: Scheme 1.9).



153

Figure 1.3: Ferrocenyl oxazoline **153** having silanol moeity.

Furthermore, application of catalytic C–H activation on other ferrocene derivatives and some other planar-chiral compounds such as paracyclophanes and cyrhetrenes were also examined.

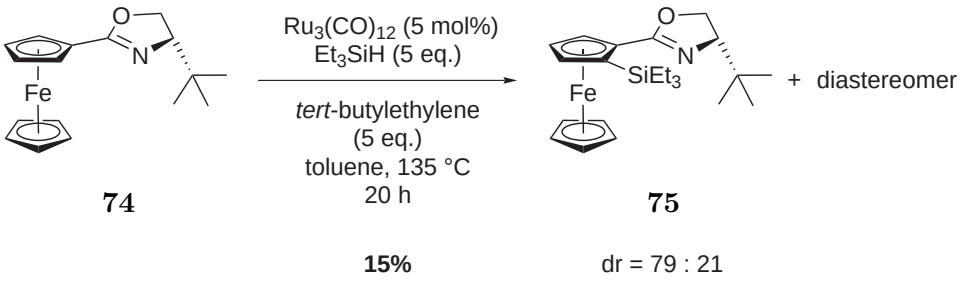
1.3 Results and Discussions

1,2-Disubstituted ferrocenes are very useful and versatile compounds due to their potential to serve as chiral ligands in asymmetric metal catalysis. [104, 105] They are commonly prepared by *ortho*-lithiation of mono-substituted ferrocenes bearing directing groups such as amines [106] or oxazolines [107] and subsequent substitution.

In this context, ferrocenyloxazoline derived from *tert*-leucine has been shown [107] to be valuable precursor for the asymmetric synthesis of 1,2-disubstituted ferrocenes. Meanwhile due to the particular interest on ferrocenyl oxazolines, as it will be described in Chapter 2, oxazoline **74** was choosen as model substrate in our study.

1.3.1 Diastereoselective C–H Activation of Ferrocenyl Oxazolines

Preliminary investigation was done with model substrate **74** under Murai's conditions (see Scheme 1.31) which have already been well established for the *ortho*-silylation of aryl oxazolines (Scheme 1.31). Expected product **75** was obtained in 15% yield with 79:21 diastereomeric ratio.



Scheme 1.31: Catalytic diastereoselective *ortho*-silylation of ferrocenyl oxazoline **74** under Murai's conditions.

After getting this promising result, different Ru-complexes, with 10 mol% catalyst loading, have been screened for optimization (Table 1.1).

Table 1.1: Screening of different metal complexes for diastereoselective *ortho*-silylation of ferrocenyl oxazoline **74**

Entry	Complex	Yield (%)	Diastereomeric ratio of silane **75**
1	$Ru_3(CO)_{12}$	15	79:21
2	$Ru(H)_2(CO)(PPh_3)_3$	36	90:10
3	$RuCl_2(CO)(PPh_3)_3$	33	90:10
4	$[RuCl_2(CO)_3]_2$	16	70:30
5	$RuCl_2(PPh_3)_4$	–	–
6	$[RuCl_2(\eta^6\text{-benzene})]_2$	–	–
7	$RhCl(PPh_3)_3$	–	–
8	$[RuCl_2(CO)_3]_2 + PPh_3$	–	–
9	$[RuCl_2(CO)_3]_2$ + dppe	–	–
10	$Ru(H_2)(H)_2(PCy_3)_2$	–	–

As it can be seen in Table 1.1, $Ru(H)_2(CO)(PPh_3)_3$ and $RuCl_2(CO)(PPh_3)_3$ were found to be the best catalysts showing same diastereoselectivity and similar efficiency (entry 2 and 3). It can be concluded that PPh_3 and CO are necessary ligands on the pre-catalyst. However, *in situ* preparation of the pre-catalyst which possess phosphine ligands failed in giving the desired product (entry 8 and 9).

Based on the poster presentation of Jenet,[15] application of $[RuCl_2(\eta^6\text{-benzene})]_2$, sodium formate and PPh_3 as a pre-catalyst mixture which increased the rate of the Murai's reaction on aryl substrates dramatically, did not afford the desired product **75**.[16]

In order to extend the scope of the reaction, various types of silanes and siloxanes have been screened by using $Ru(H)_2(CO)(PPh_3)_3$ as catalyst. The results are shown in Table 1.2

Table 1.2: Screening of different silanes for diastereoselective *ortho*-silylation of ferrocenyl oxazoline **74** by using $Ru(H)_2(CO)(PPh_3)_3$ as catalyst.

Entry	Silanes Source	Yield (%)	Diastereomeric ratio of silane **75**
1	Et_3SiH	33	90:10
2	Et_2MeSiH	25	87:13
3	$Me_2SiH\text{-}O\text{-}SiHMe_2$	–	–
4	$CH_2 = CH\text{-}Si(OEt)_3$	–	–
5	$CH_2 = CH\text{-}Si(Me)_3$	–	–
6	$CH_2 = CH\text{-}CH_2Si(Me)_3$	–	–
7	$PhSiH_3$	–	–
8	$PhMe_2SiH$	–	–
9	Et_2SiH_2	–	–
10	$(EtO)_2MeSiH$	–	–
11	$(EtO)Me_2SiH$	–	–

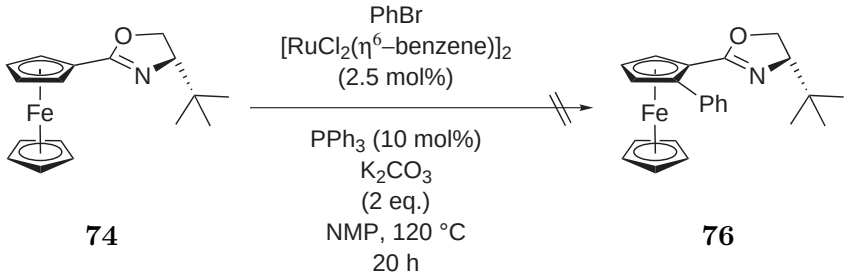
As a result of this study, it could be concluded that trialkyl silanes were necessary to succeed and alkoxy or alkoxy-alkyl silanes do not react at all.

Based on the work by Oi [108] (see Scheme 1.32), Ru-catalyzed *ortho*-phenylation of oxazoline

[15] The third Lilly European Distinguished Lectureship, November 24, 2005.

[16] Triethoxyvinylsilane was also tested under these conditions, but gave no product.

74 was also tested. Unfortunately, treatment of oxazoline **74** with bromobenzene in the presence of 2.5 mol% of $[RuCl_2(\eta^6\text{-benzene})]_2$, 10 mol% of PPh_3 and 2 equivalent of K_2CO_3 in NMP at 120 °C did not afford the desired product **76** (Scheme 1.32).



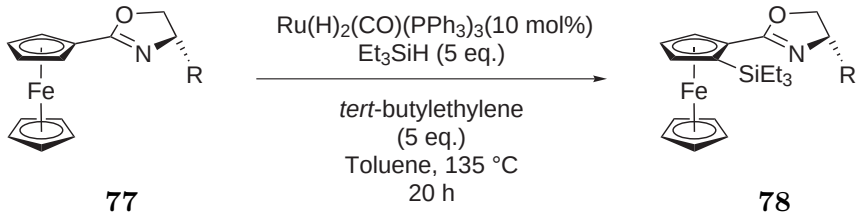
Scheme 1.32: Catalytic diastereoselective *ortho*-silylation of ferrocenyl oxazolines **77**.

Additional optimization were performed in regard to the solvent and hydrogen scavenger (Table 1.3). In agreement with Murai's results, [34] norbornene and *tert*-butylethylene showed very similar activity but norbornene gave lower diastereoselectivity (entry 2). By using *o*-xylene as solvent, the reaction did not proceed at all (entry 3). Performing the reaction in the absence of solvent gave better yield but slightly lower diastereoselectivity (entry 4). Using 15 mol% of catalyst resulted in an increase of yield up to 60%, but a slight decrease in diastereomeric ratio to 88:12.

Table 1.3: Optimization of solvent and hydrogen scavenger for diastereoselective *ortho*-silylation of ferrocenyl oxazoline **74** by using $Ru(H)_2(CO)(PPh_3)_3$ as catalyst.

Entry	Solvent	H-Scavenger	Yield (%)	Catalyst	dr of silane **75**
1	toluene	*tert*-butyl ethylene	10	36	90:10
2	toluene	norbornene	10	34	78:22
3	*o*-xylene	*tert*-butyl ethylene	10	–	–
4	–	*tert*-butyl ethylene	10	43	87:13
5	toluene	*tert*-butyl ethylene	15	60	88:12

Varying the substituents on oxazoline group gave following results shown in Scheme 1.33 and Table 1.4



77 **78**

Scheme 1.33: Catalytic diastereoselective *ortho*-silylation of ferrocenyl oxazolines **77**.

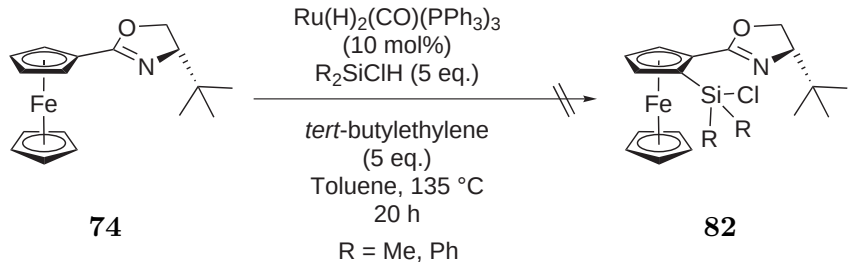
Table 1.4: Catalytic diastereoselective *ortho*-silylation of ferrocenyl oxazolines **77**

Entry	R	Compound	Yield (%)	Diastereomeric ratio
1	*i*-Pr	**79**	60	62:38
2	Ph	**80**	65	60:40
3	CH_2Ph	**81**	72	58:42

As seen in Table 1.4, the substituents on oxazolines have a substantial effect on yield and diastereomeric ratio. *iso*-Propyl substituent increased the yield of the reaction but decreased dramatically diastereomeric ratio. Phenyl and benzyl substituents have positive effect on yields but negative effect on diastereomeric ratio. As a result, having a less bulky group like benzyl substituent caused an increment in yield, but a dramatic decrease in diastereomeric ratio.

After establishing this result on *ortho*-silylation of ferrocenyl oxazoline **77** with triethylsilane, since alkoxysilanes do not react under these reaction conditions, utilization of chlorosilanes could be an alternative pathway in order synthesize silanols **153**. However, neither dimethylchlorosilane nor diphenylchlorosilane gave the desired chlorosilane products **82** but only starting material. This might be due to the instability of chlorosilane moeity in the presence of oxazoline group which might react internally with Si–Cl bond and breaking the C–Si bond to form the starting material back. These results which are also consistent with those that will be presented in Scheme 2.18, appearently show that chlorosilanes **82** are sensitive compounds and not so easy to synthesize (Scheme 1.34).[17]

[17]Quenching the reaction mixture after 20 h with a Grignard reagent such as MeMgBr was also not helpful to isolate any C–H activated product.



Scheme 1.34: Unsuccesful attempt to synthesize chlorosilane **82** *via* C–H activation.

1.3.2 Application of Different Type of Substrates

Applying different directing groups than oxazoline was the subsequent target of the project. For that purpose a series of different ferrocene derivatives was utilized for the *ortho*-silylation reaction under optimized conditions (Figure 1.4).

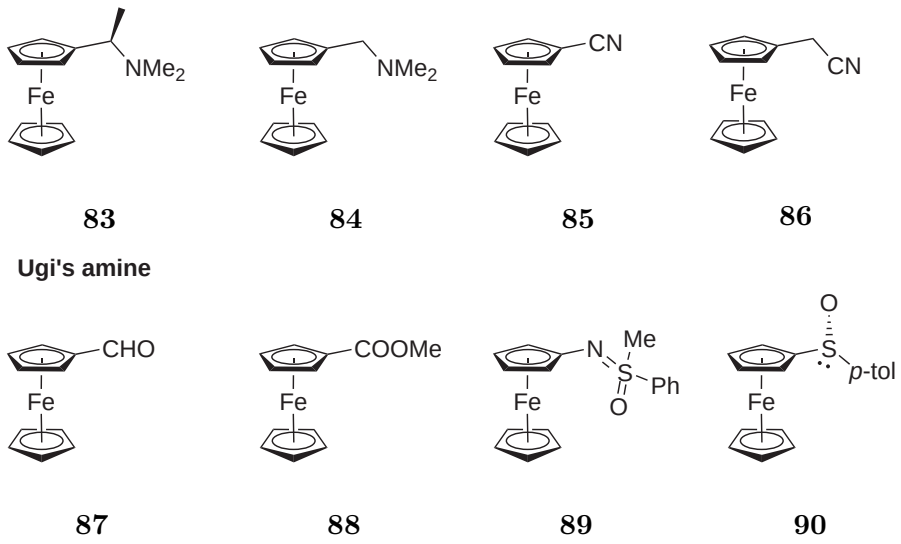
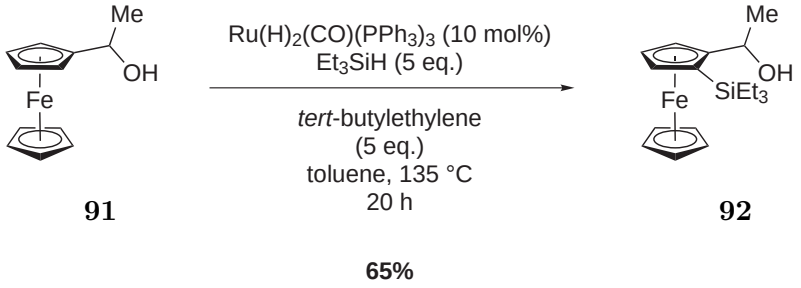


Figure 1.4: Different ferrocene derivatives having different directing groups which have been tested under Murai's conditions for *ortho*-silylation with Et_3SiH.

However, none of these ferrocene derivative afforded *ortho*-silylation product under Murai's conditions.

On the other hand, when ferrocenyl alcohol **91** was tested under Murai's conditions, *ortho*-silylated product **92** was obtained in moderate yields (Scheme 1.35).

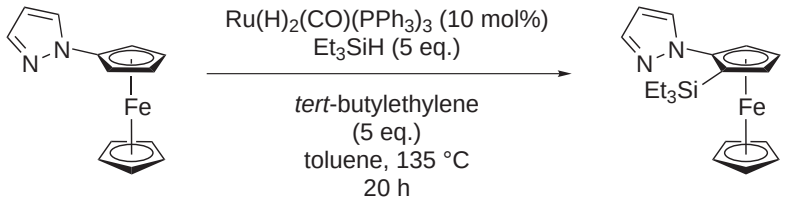


91 **92**

65%

Scheme 1.35: Ru-catalyzed *ortho*-silylation of ferrocenyl alcohol **91** *via* C–H activation.

N-ferrocenyl pyrazole (**93**) was treated with triethylsilane and tert-butylethylene in the presence of ruthenium catalyst in toluene to afford *ortho*-silylated product in low yield (Scheme 1.36).

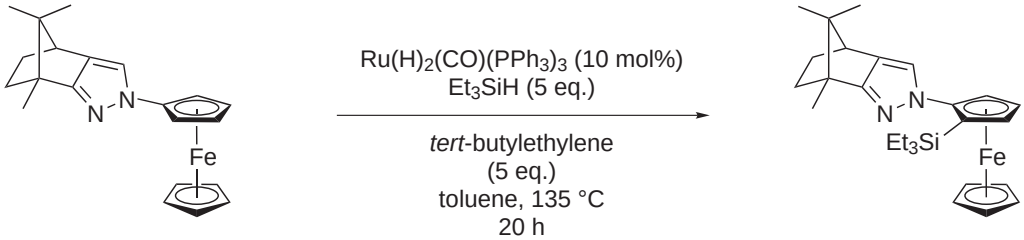


93 **94**

35%

Scheme 1.36: Ru-catalyzed *ortho*-silylation of ferrocenyl pyrazole **93** *via* C–H activation.

Chiral derivative of ferrocenyl pyrazole **95**[18] was also tested under the same conditions and the desired product **96** was obtained in low yield and moderate diastereomeric ratio (Scheme 1.37).



95 **21%** **96**

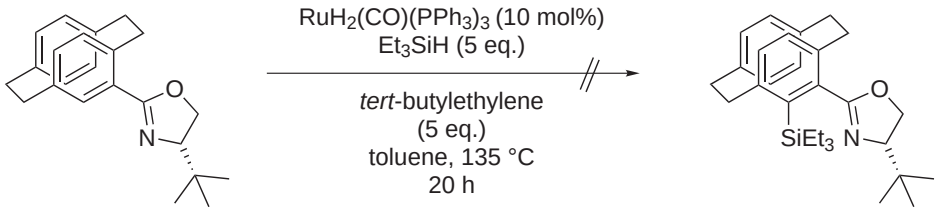
dr = 73:27

Scheme 1.37: Ru-catalyzed *ortho*-silylation of ferrocenyl chiral pyrazole **95** *via* C–H activation.

Apart from ferrocene, some other backbones have also been tested in the Ru-catalyzed *ortho*-

[18]For the synthesis of ferrocenyl pyrazoles **93** and **95**, see: Table 3.4.1

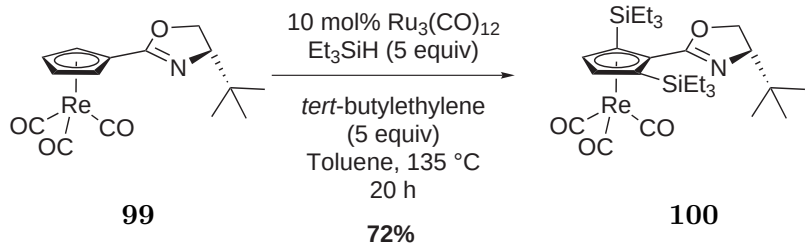
silylation reaction. For example, paracyclophanes are difficult compounds to perform *ortho*-lithiation by using strong bases such as *n*-BuLi or *sec*-BuLi. Lithiation on the benzylic position was preferred and it is not so easy to perform *ortho*-substitution reactions on paracyclophanes. [109] Therefore paracyclophanyl oxazoline **97** was tested for Ru-catalyzed ortho-silylation via C–H activation under Murai's conditions. However, the reaction did not take place and the desired product **98** has not been obtained.



97 **98**

Scheme 1.38: Ru-catalyzed C–H activation of paracyclophanyl oxazoline **97** *via* C–H activation.

On the other hand, application of cyrhetrenes in C–H activation reaction as another planar-chiral substrate backbone gave some unexpected results. Ru-catalyzed *ortho*-silylation of cyrhetrenyl oxazoline **99** afforded the double silylated product **100** as single product in high yield. Surprisingly, even when one equivalent of triethylsilane was used, the double silylated product **100** was isolated beside starting material.

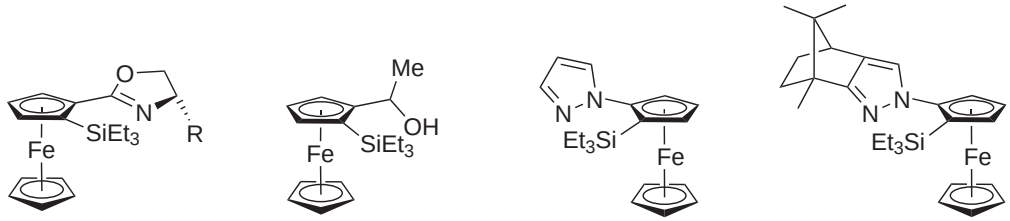


99 **100**

Scheme 1.39: Ru-catalyzed double silylation of cyrhetrenes oxazoline **99** *via* C–H activation.

1.4 Summary and Outlook

In the present thesis, a Ru-catalyzed diastereoselective *ortho*-silylation of ferrocenyl oxazolines **77** was achieved in poor to good yields and moderate to high diastereomeric ratios. To the best of our knowledge, this is the first catalytic and diastereoselective C–H activation on ferrocenes. After screening many other directing groups, only ferrocenyl ethanol **91** and pyrazoles **93** and **95** furnished the desired *ortho*-silylated product. Crythrenyl oxazoline **99** afforded double silylated product, probably, due to the electron deficiency on Cp ring which activates the ring towards C–H activation reactions.



78 **92** **94** **96**

up to dr = 90:10 dr = 73:27

Figure 1.5: C–H activation on ferrocenes.

Unfortunately, utilization of other silane sources, which could be further functionalized easier that triethylsilyl group, was not possible. Therefore, the synthesis of silanol **153** could not be achieved *via* C–H activation rather than conventional method, that is *ortho*-lithiation.

Chapter 2

Organosilanols

Silicon is the second most abundant element in the earth's crust and seventh most plentiful element in the universe. In nature, silicon exists primarily as silicates, aluminosilicates and silica. The latter of which is the raw material used for the industrial production of silicon compounds. Such processes tend to be both difficult and expensive, mostly due to the thermodynamic stability of the Si–O bonds of silica and because there are only a limited number of methods by which to replace oxygen with another element such as carbon. Somewhat surprisingly, given its relationship to carbon on the periodic table, organosilicon compounds are rarely found in nature. This is perhaps reflected in the fact that organosilicon species cannot be formed directly from silica, but instead are invariably synthesized from the more reactive halosilanes.

Some of the more commonly synthesized organosilicon compounds are the organosilanols. The most common ones are simple silanols of the type R_3SiOH, which are analog to carbinol, silanediols and silanetriol of the types $R_2Si(OH)_2$ and $RSi(OH)_3$, respectively, are also well known. The silanol moiety is, in fact, ubiquitous in nature because, the aquatic environment contains very low level of dissolved silicic acid $Si(OH)_4$ and the many varieties of silica, SiO_2, and silicate rocks have surface hydroxyl groups. However, it was not until 1871 that the first procedure for the preparation of an organosilanol was reported by Ladenburg [110], who synthesized Et_3SiOH, by the hydrolysis of Et_3SiCl with aqueous ammonia. Since this seminal discovery, organosilanols have featured widely in chemical synthesis.

2.1 Properties of Organosilanols

2.1.1 Acidity and Basicity of Organosilanols

On the high reactivity and acidity of silanols was first commented in 1946 when it was found that Et_3SiOH reacted readily with sodium in xylene and that the silanolate, Me_3SiONa, was formed rapidly when the same silanol was treated with 12 mol/L NaOH solution. Triethylsilyl acetate was also synthesized from the triethylsilanol and acetic anhydride in good yields. These observations have been summarized by Sommer [111] as following:

> *'This surprising behaviour of trimethylsilanol as an acid toward alkali, the activity of both silanols with sodium, and the formation in good yield of triethylsilyl acetate from the silanol and acetic anhydride, are evidence that the hydrogen of the hydroxyl in trialkylsilanols is much more reactive than that in tertiary alcohols.'*

Many subsequent studies, mainly using IR, NMR spectroscopy and acid-base titration, have confirmed the relatively high acidity of silanols compared with carbinols. Surprisingly, silanols are nearly as basic as the alcohols despite the fact that they are much more acidic. That the silanols are of an amphoteric nature has been rationalized by invoking $p\pi$-$d\pi$ bonding between Si and O, which allows the negative charge of an R_3SiO^- ion to be delocalized, thus giving an enhanced acidity, whilst the lone pairs of electrons on the oxygen atom, afford silanols their basic properties. In view of the high acidity and the relatively high basicity of silanols, it is to be expected that they will form strong hydrogen bonds both with themselves and with other suitable species.

2.1.2 Biologically Active Silanols

Silanols as Drug Candidate Analogs

The replacement of carbon atoms with silicon is a strategy for extending the chemical diversity in a known series of organic drugs and for providing potential access to new pharmaceuticals, particularly as the bond between silicon and an sp^2- or sp^3-hybridized carbon atom is stable under most physiological conditions. Tacke has reported many articles concerning this topic and some examples, concerning the interchange of carbinols (R_3COH) with silanols (R_3SiOH) that are taken largely from his research, are presented in the following paragraphs.

A substantial series of muscarinic antagonists, perhaps best-illustrates what can be achieved by this apparently simple carbon/silicon switch. The structure activity relationships (SARs)

of muscarinic antagonists with the enzyme active sites have been extensively studied, and it is clear that the central carbinol moiety common to each of the carbon analogs of the compounds presented in Figure 2.1 is essential for their activity. Changing the carbinol groups with silanols, which are more acidic, might enhance the receptor binding. Indeed, most of the silanols shown in Figure 2.1 demonstrate higher affinities for muscarinic receptors than do their carbon analogs.

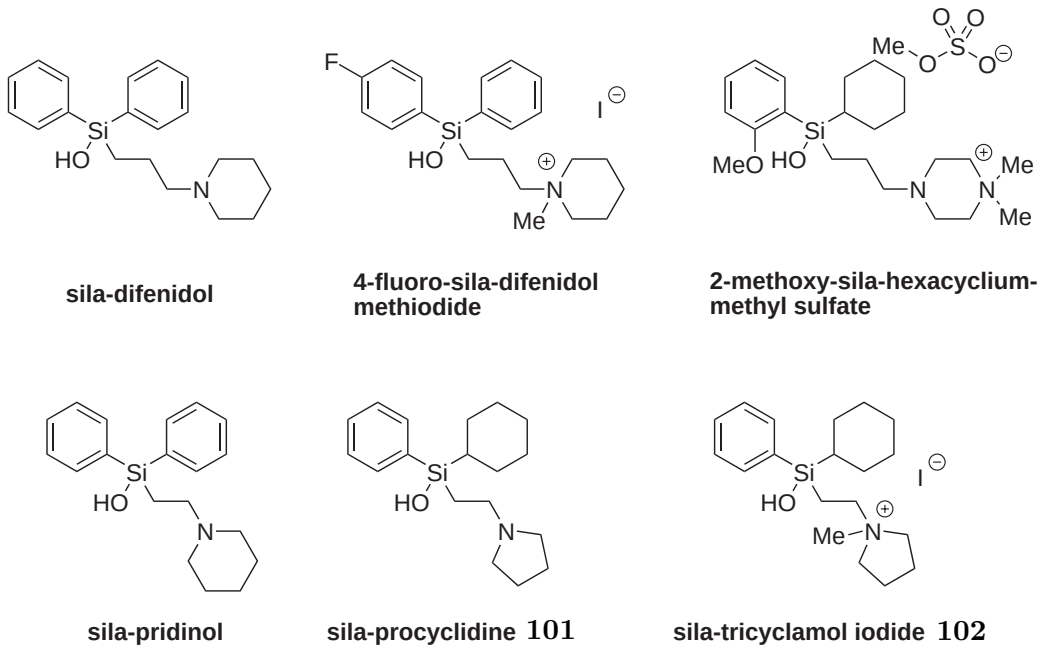
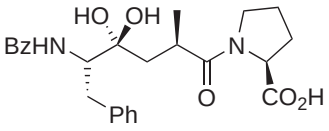


Figure 2.1: Some silanols having anti-muscarinic activity.

Some silanols have also been studied for their *in vivo* properties, and the results obtained clearly demonstrate their efficacy. For example, *in vivo* studies of the peripheral and central anticholinergic effects of orally administered sila-procyclidine (**101**) and sila-tricyclamol iodide (**102**) upon mice showed that the silicon analog had a greated physiological effect than its carbon counterpart. In addition to demonstrating greater potency, silaprocyclidine has a longer duration of action at equivalent dose. [112] However, silanols having chirality on silicon were, unfortunately, not able to be developed as single enantiomer drug candidates because, unlike the parent carbon compounds, the analog silanols undergo a relatively rapid racemization under physiological conditions. However, enantiomers of (hydroxymethyl)silanes have been showen to demonstrate configurational stability under physiological conditions[1].

[1]For a book about organosilicon chemistry including chirality in bioorganosilicon chemistry, see: ref. [113]

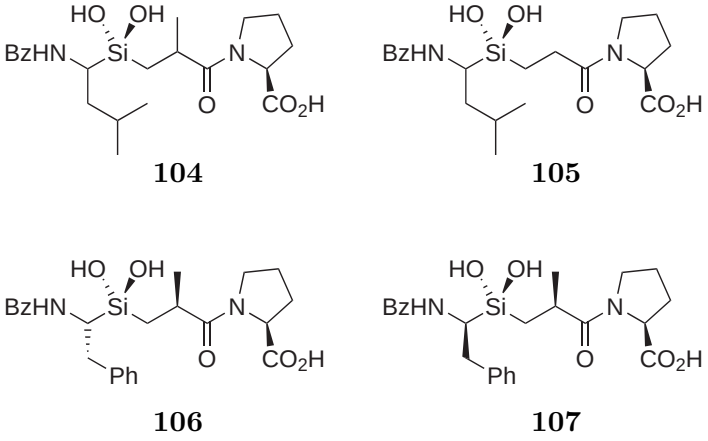


103

Almquist's ketone
(*shown hydrated*)

Figure 2.2: Hydrated form of Almquist's ketone.

Silanediols are isosteric with the unstable hydrated carbonyl group. Sieburth reported [114] the first use of silanediols as a transition state analog, which were found to emulate the hydrated form of Almquist's ketone. Almquist's ketone, when in its energetically disfavored hydrate form **103** (Figure 2.2) serves to inhibit ACE (angiotensin converting enzyme) with an IC_{50} value of 1.0 nM, presumably through chelation of zinc at the active site of this metal metalloproteas inhibitor. Enzyme assay studies demonstrated that silanediols **104** and **105** are capable of chelating the zinc ion at the active site of ACE, with IC_{50} values of 14 and 57 nM, respectively. Two years later, Sieburth additionally reported [115] that the silanediol derivatives **106** and **107** of Almquist's ketone also show activity as ACE inhibitors with IC_{50} values of 3.8 and 19 nM, respectively. These results show that the silanediols moiety can serve as an effective functional group with which to mimic the transition state of metalloprotease inhibitors (Figure 2.3).[2]



104 **105**

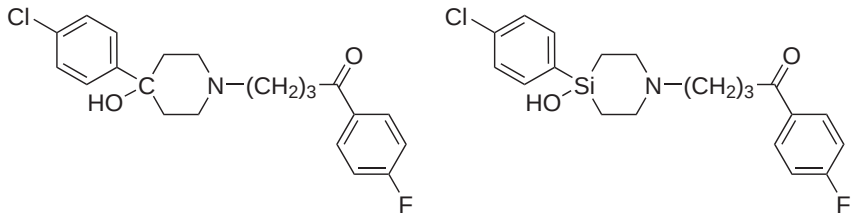
106 **107**

Figure 2.3: Silicon analogs of Almquist's ketone as ACE inhibitors.

Recently, Tacke reported [117] the synthesis of the silicon analog of the dopamine (D2) receptor antagonist, haloperidal. In radioligand binding studies, carbon and silicon analogs

[2]Very recently, Sieburth reviewed [116] his contributions on this topic

showed similar potencies at recombinant human dopamine hD1, hD4 and hD5 receptors, whereas the silicon analog, sila-haloperidal, was found to be 4.7-fold more potent at hD2 receptors than the corresponding carbon analog (Figure 2.4).



haloperidal **sila-haloperidal**

Figure 2.4: The structure of haloperidal and sila-haloperidal.

Very recently, Tacke published [118] another example in which a silicon analog of a biologically active carbinol *rac*-venlafaxine, was synthesized in order to compare its pharmacological efficacy with that of its carbon counterpart (Figure 2.5). *rac*-Venlafaxine is a serotonin/noradrenaline reuptake inhibitor which was found clinical use as antidepressant. Its silicon analog *rac*-sila-venlafaxine, was produced in multistep synthesis, and tested as racemic and enantiomerically pure form of its hydrochloride salts for their efficacy in serotonin, noradrenaline and dopamine reuptake inhibition assays (Figure 2.5). These pharmacological studies of the enantiomerically pure compounds showed that while activity of the noradrenaline and dopamine transporters is essentially unaffected by sila-substitution, the potency at serotonin transporters is reduced by two orders of magnitude. Similar activities were observed against different transporters, when the racemates of venlafaxine and sila-venlafaxine were tested.

***rac*-venlafaxine** ***rac*-sila-venlafaxine**

Figure 2.5: The structure of *rac*-venlafaxine and *rac*-sila-venlafaxine.

Silanols as Perfumes

α-Terpineol is a component of many ethereal oils with the fragrance of lilac. Wannagat reported [119] the synthesis of sila-derivative of α-terpineol and found that the intensity of the fragrance of sila-α-terpineol is comparable with the natural product. (Figure 2.6).

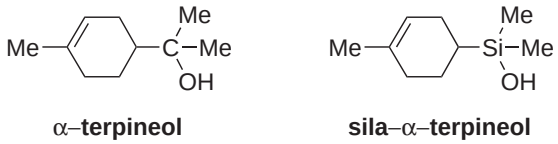


Figure 2.6: The structure of α-terpineol and its sila-derivative.

Linalool is a widespread natural product with a muguet-like fragrance, and (S)-(+)-enantiomer of which a sex pheremone acting upon males of the vernal solitary bee species *Colletes cunicularius*. Tacke also synthesized [120] the sila-derivative of *rac*-linalool and demonstrated that there is no big difference between the activity of the natural pheromone and its sila-analog (Figure 2.7).[3]

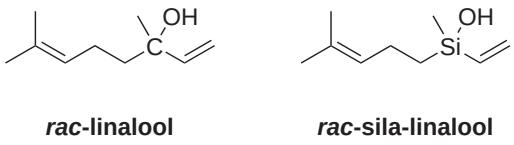


Figure 2.7: The structure of *rac*-linalool and its sila-derivative.

2.2 General Synthesis of Organosilanols

Silanols are generally sensitive to acid, base and heat because they may undergo dimerization to form siloxanes *via* self-condensation. This point should be considered when planning the synthesis and isolation of a silanol. The use of dilute solutions for the synthesis might be helpful to prevent the dimerization. In the reaction mixture for the synthesis of silanols, formation of an acid or base should be avoided, otherwise precautions, such as *in situ* neutralization by adding a weak acid or base, must be taken. The reactions should not be carried out at high temperatures. Bulky substituents on silicon reduce the tendency of dimerization due to the

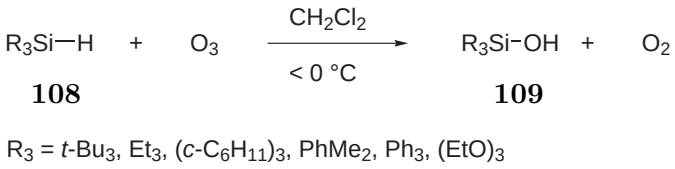
[3] In the analysis of activity, antennae of males of the bee species C. cunicularius were used as detectors.

steric factors. However, these substituents also cause the lower reactivity of the silicon atom towards hydrolysis or oxidation and may require harsh conditions to be reacted.

2.2.1 Synthesis of Silanols From Si–H Compounds

Organosilanes containing small substituents and several Si–H bonds such as $RSiH_3$ (R = Me, Et, *n*-Bu) species are very reactive towards oxygen. They may spontaneously ignite in air, in the presence of a metal or under pressure. On the other hand, organosilanes possessing bulkier substituents or fewer Si–H bonds are more stable and may be distilled in air.

Compounds containing Si–H bonds can be rapidly oxidized by ozone at low temperatures to afford the corresponding silanols (and oxygen) in good yields. Ozonolysis of the sterically hindered silane *t*-Bu_3SiH gave *t*-Bu_3SiOH as the only detectable product. As shown in Scheme 2.1, many other trisubstituted organosilanes **108** having the phenyl or ethoxy groups can also be readily converted to silanols **109** easily.[4]



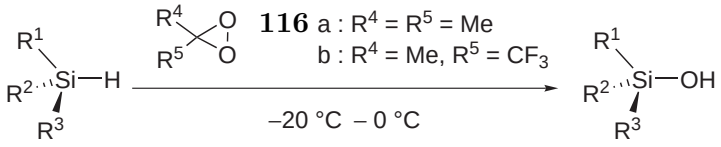
Scheme 2.1: Oxidation of trisubstituted silanes **108** to corresponding silanols **109** with ozone.

Interestingly, oxidation of triethylsilane with ozone afforded singlet dioxygen in addition to the triethylsilanol, presumably *via* formation of the intermediate triethylsilyl hydrotrioxide, $Et_3SiOOOH$. This reaction has been investigated by Corey [122] since it seemed that oxidation of triethylsilane with ozone could be exploited as a chemical source of singlet oxygen at sufficiently low temperatures as to allow the synthesis of endoperoxides.

Another method for the oxidation of the Si–H bond employs highly reactive dioxiranes. This method has the advantages of relatively short reaction times and high yields whilst additionally producing fewer producing less by-products, and has found greatest application in synthesis where low temperatures and the absence of acids or bases are required for the formation of otherwise sensitive compounds. Adam reported [123] a very efficient oxidation of silanes to silanols with dioxirane at low temperatures, in which, for example, dioxirane **116a** reacts with Et_3SiH (**110**) and $PhMe_2SiH$ (**111**) in less than one minute at between −20 °C and 0 °C, to

[4] For a mechanistic study on this topic, see: ref. [121]

afford the correspondins silanols **113** and **114** in almost quantitative yields. The optically active silane (+)(α-naphthyl)PhMeSiH ((+)-**112**) may be transformed with a high degree of retention to the corresponding silanol (+)-**115** (Scheme 2.2), and as a result, a concerted spiro-type transition structure has been proposed for this Si–H bond oxidation.

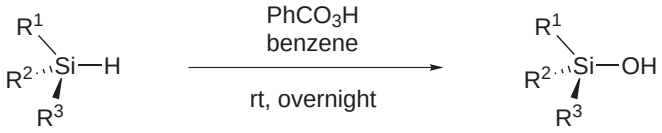


110: $R^1 = R^2 = R^3 = Et$
111: $R^1 = Ph$, $R^2 = R^3 = Me$
112: $R^1 = \alpha$-naphthyl, $R^2 = Ph$, $R^3 = Me$

113 : $R^1 = R^2 = R^3 = Et$
114 : $R^1 = Ph$, $R^2 = R^3 = Me$
115 : $R^1 = \alpha$-naphthyl, $R^2 = Ph$, $R^3 = Me$

Scheme 2.2: Oxidation of trisubstituted silanes to corresponding silanols with dioxiranes **116**.

In 1967, Nagai reported [124] a novel method for the oxidation of silanes to silanols with peroxybenzoic acid to afford corresponding silanols. By way of example, Et_3SiH (**110**), $PhMe_2SiH$ (**111**) and Ph_2MeSiH (**117**) each react with peroxybenzoic acid in benzene to afford the corresponding silanols **113**, **114** and **118** in 70, 60 and 58% yields, respectively (Scheme 2.3). This kind of oxidation has been shown to proceed with retention of configuration at silicon. [125]



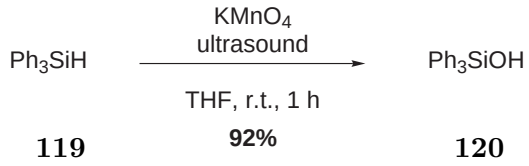
110: $R^1 = R^2 = R^3 = Et$
111: $R^1 = Ph$, $R^2 = R^3 = Me$
117: $R^1 = R^2 = Ph$, $R^3 = Me$

113 : $R^1 = R^2 = R^3 = Et$
114 : $R^1 = Ph$, $R^2 = R^3 = Me$
118 : $R^1 = R^2 = Ph$, $R^3 = Me$

Scheme 2.3: Oxidation of trisubstituted silanes to corresponding silanols with peroxybenzoic acid.

Oxidation of Si–H bonds may also be carried out by use of the strong oxidizing agent, $KMnO_4$. Lickiss reported [126] that the use of ultrasound in experiments employing $KMnO_4$ for the oxidation of silanes increased the solubility of the oxidant in organic solvents, thereby improving the yield and decreasing the reaction time, particularly for the oxidation of sterically hindered Si–H bonds. For instance, conventional stirring of Ph_3SiH (**119**) with $KMnO_4$ in THF furnished the corresponding silanol **120** in 88% yield after 22 h, whereas utilization of ultrasound

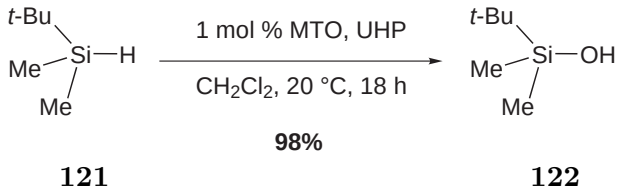
for only one hour gave the same product in up to 92% yield (Scheme 2.4). it should be noted, however, that when the steric hindrance is too great, as, for example, in $(Me_3Si)_3CPh_3SiH$, no reaction occurs.



Scheme 2.4: Ultrasound-assisted oxidation of triphenylsilane (**119**) triphenylsilanol (**120**) with $KMnO_4$.

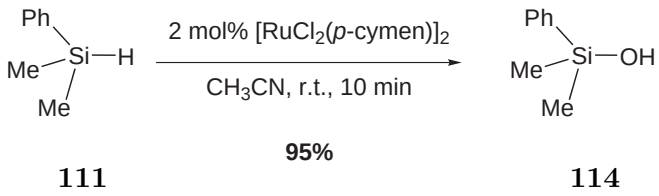
Although, regarded as relatively expensive, silver salts such as $AgNO_3$ and Ag_2O can also be used in stoichiometric amounts for the otherwise clean and generally high yielding oxidation of silane. [127]

In recent years, research into the oxidation of silanes to silanols has increasingly focused on metal catalyzed processes, such that many new methods have been developed. One of the earliest examples of metal catalyzed silane oxidation to be reported was developed by Adam who discovered that the methyltrioxoruthenium (MTO) effects the oxidation of silanes in high conversions and excellent selectivities in favor of the silanols without the formation of disiloxane by-products) when the urea/hydrogen peroxide adduct (UHP) is used as oxygen source instead of aqueous H_2O_2. It is proposed that the urea acts as a host, forming channels, inside which the MTO-catalyzed Si–H oxidation reaction takes place. [128] Under these heterogeneous conditions, the catalyst is not inly stabilized but the self-condensation of silanols is also prevented for steric reasons, meaning that a bulky silane such as *t*-$BuMe_2SiH$ (**122**) can be converted into the corresponding silanol **122** at room temperature in very high yield after 18 h (Scheme 2.5). This type of oxidation proceeds with retention of stereochemistry at silicon.



Scheme 2.5: MTO-catalyzed oxidation of silane **121** to silanol **122** with UHP at room temperature.

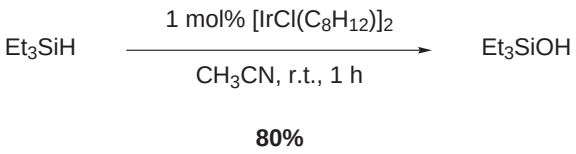
In 2000, Chang reported [129] a further notable advance in this area through his discovery of a practical, highly selective hydrolytic and catalytic oxidation method that is applicable to a wide variety of silane substrates. With a low catalyst loading (2 mol%) of $[RuCl_2(p\text{-cymen})]_2$, in the presence of two equivalents of water at room temperature under air, phenyldimethylsilane (**111**) can be oxidized to phenyldimethylsilanol (**114**) in 95% yield after only 10 minutes at room temperature (Scheme 2.6). Although the exact role of oxygen is not known at this stage, the reaction rates were moderately increased under an oxygen atmosphere especially in cases of slow-reacting substrates. Without water, less than 5% conversion was observed under these reaction conditions. The oxidation of an optically active silane proceeds with inversion of configuration at silicon.



111 **114**

Scheme 2.6: Ru-catalyzed oxidation of phenyldimethylsilane (**111**) to phenyldimethylsilanol (**114**) under mild conditions.

Very recently, Chang has improved his procedure with a catalyst system of $[IrCl(C_8H_{12})]_2$ under essentially-neutral and mild conditions, and a wide variety of silanols have been synthesized in good to excellent yields. [130] For example, when a solution of triethylsilane in acetonitrile is treated at room temperature with 2 equivalents of water and 1 mol% $[IrCl(C_8H_{12})]_2$, triethylsilanol is produced in 80% yield after 1 h (Scheme 2.7).



Scheme 2.7: Ir-catalyzed oxidation of triethylsilane to triethylsilanol under mild conditions.

Although the mechanism of the oxidation of silanes to silanols in the presence of $[IrCl(C_8H_{12})]_2/H_2O$ or $[RuCl_2(p\text{-cymen})]_2/H_2O$ system is not definitely declared by the author but it is assumed that the Ir or Ru metals activate the Si–H bond to give a silylmetal hydride intermediate because peaks at –8.51 ppm and at –10.00 ppm were observed in separate ^{1}H-NMR spectroscopy ex-

periments upon mixing the triethylsilane with stoichiometric amounts of $[IrCl(C_8H_{12})]_2$ and $[RuCl_2(p\text{-cymen})]_2$ (in CD_3CN), respectively. The oxidation of an optically active silane proceeds with racemization at the silicon centre.

2.2.2 Synthesis of Silanols by the Hydrolysis of Halosilane

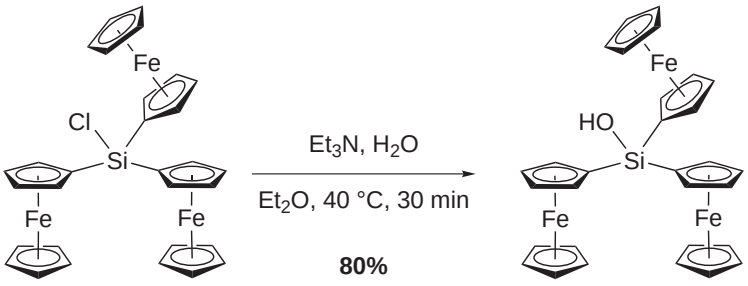
Si–X bonds are generally labile and sensitive to hydrolysis. Therefore, one of the easy and common way to obtain silanols is the hydrolysis of Si–X bond under various conditions depending on the substrate.

Synthesis of silanols by the hydrolysis of Si–F bond

The hydrolysis of fluorosilanes is not a commonly used method for the synthesis of silanols. It requires alkaline conditions; thus, i-Pr_3SiF and i-Pr_2SiF_2 may react with aqueous ethanolic sodium or potassium hydroxide solutions to afford the corresponding silanols i-Pr_3SiOH and i-$Pr_2Si(OH)_2$ in 65 and 50% yields, respectively. [131] Although not a hydrolysis reaction, a similar protocol has been used for the formation of sterically hindered silanols in which for example, t-Bu_2SiMeF reacted with KOH in refluxing hexane to give t-$Bu_2MeSiOH$ in 78% yield. [132]

Synthesis of silanols by the hydrolysis of Si–Cl bond

In contrast, chlorosilanes are perhaps, one of the most commonly employed substrates for the synthesis of silanols due to their ready availability and susceptibility towards hydrolysis, however, some precautions should be taken to prevent the dimerization of silanols in aqueous media by the addition of inorganic or organic bases to the reaction mixture in order to neutralize any hydrochloric acid formed. This procedure is nicely illustrated for the hydrolysis of Et_2SiCl_2 with aqueous NaOH, which produces $Et_2Si(OH)_2$ in good yields (65%). [133] Chlorosilanes with bulky substituents like ferrocene can also be hydrolyzed in this manner, such that, for example, when a solution of triferrocenylchlorosilane (**123**) in diethylether was reacted with H_2O in the presence of Et_3N at 40 °C, triferrocenylsilanol (**124**) was afforded in 80% yield (Scheme 2.8). [134]



123 **124**

Scheme 2.8: Synthesis of Fc_3SiOH by the hydrolysis of Fc_3SiCl.

Synthesis of silanols by the hydrolysis of Si–Br and Si–I bonds

The hydrolysis of bromosilanes is rarely used for the synthesis of silanols, but such substrates may be hydrolyzed in similar ways to chlorosilanes. For example, the hydrolysis of i-Pr_2SiBr_2 with aqueous ammonia gives i-$Pr_2Si(OH)_2$ in 90% yield. [135]

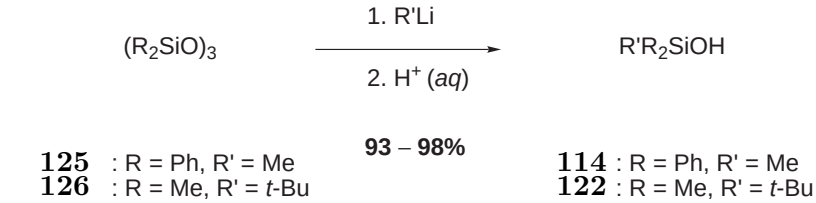
Although, the hyrolysis of iodosilanes is generally relatively fast, the presence of bulky groups on silicon atom may hamper silanol formation, such that, lengthy reaction times are sometimes necessary to attain hydrolysis. For instance, $(Me_3Si)_3SiPh_2I$ requires 60 days under reflux in H_2O/MeCN (1:19) to be hydrolyzed. [136, 137] whereas, the less sterically hindered dimethyl derivative, $(Me_3Si)_3SiMe_2I$, has a half-life of 19 minutes in H_2O/DMF (1:49) at 60 °C. The hydrolysis of $(Me_3Si)_3SiHFI$ with H_2O/acetone (1:1) affords $(Me_3Si)_3SiHFOH$ in 2 h at room temperature in 88% yield, and demonstrates the relative ease of hydrolysis of Si–I compared with both Si–H and Si–F bonds.

2.2.3 Synthesis of Silanols *via* the Cleavage of Si–O Bond

The hydrolysis of alkoxysilanes provides an alternative approach to synthesis of silanols that allows for the formation of products (such as those containing non-bulky functional groups) which would otherwise be susceptible to dimerization. For example, shaking of $Me_2Si(OEt)_2$ with H_2O at 25 °C for 48 h affords crystalline $Me_2Si(OH)_2$, which is very sensitive towards both acids and bases and may undergo condensation to give dimethyl disiloxane. [138]

An analogous approach to the formation of silanols from alkoxy silanes is illustrated by the cleavage of the Si–O bond of cyclic siloxanes, *e.g.*$(R_2SiO)_3$, with organolithium reagents. For example, the reaction of MeLi and $(Ph_2SiO)_3$ (**125**) in hexane at room temperature afford a

93% yield of $Ph_2MeSiOH$ (**114**) upon acidic work-up, while *t*-BuLi and $(Me_2SiO)_3$ (**126**) in diethylether at between 0 °C and room temperature furnish *t*-$BuMe_2SiOH$ (**122**) in 98% yield (Scheme 2.9). [139]



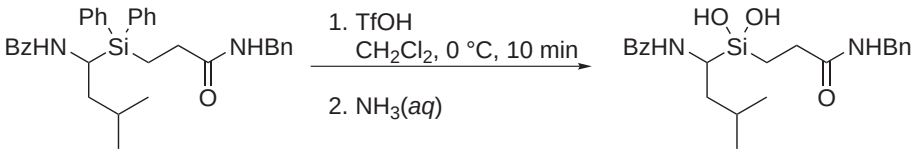
Scheme 2.9: Synthesis of silanols *via* the ring opening of siloxanes with organolithium reagents.

2.2.4 Synthesis of Silanols by the Hydrolysis of Si–N Bond

Silanols have also, on occasion, been prepared by the hydrolysis of silanes that posses Si–N bond. For example, trimethylsilanol was obtained in 73% yield by the hydrolysis of $Me_3SiNHAc$ in ice-cold water after 30 min. [140] It would appear that aminosilanes are more susceptible to hydrolysis that are alkoxysilanes, since Miner found that it is possible to remove the NH_2 groups, but not the *tert*-alkoxy groups of $(t\text{-BuO})_2Si(NH_2)_2$ and afford white needle-like crystals of $(t\text{-BuO})_2Si(OH)_2$ in 56% yield after shaking in ice water over 5 min. [141]

2.2.5 Synthesis of Silanols by the Cleavage of Si–Ph Bond

The cleavage of Si–Ph bond can also be used to generate silanols. As shown in Scheme 2.10, Sieburth reported [114] that the hydrolysis reaction of diphenylsilane **127** to silanediol **128** were performed using triflic acid at 0 °C for 10 min, followed by addition of aqueous ammonia solution.



127 **128**

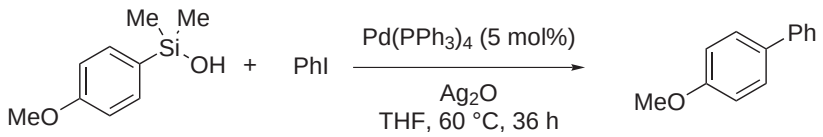
Scheme 2.10: The hydrolysis of Si–Ph bond to synthesize silanediol **128**.

As represented in this section, silanols can be synthesized by many various methods which are also a consequence of their varied applications in organic chemistry.

2.3 Application of Silanols

2.3.1 Cross-coupling Reactions of Silanols

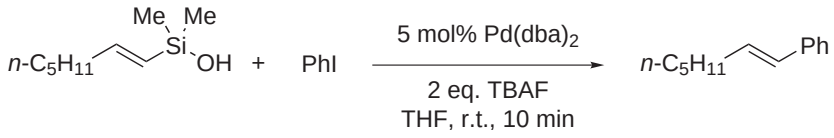
Since silanols are inexpensive, readily prepared and environmentally benign, they have also found application as coupling components in cross-coupling reactions. In 1999, Mori reported [142] that aryl- and alkenylsilanols can undergo Mizoroki-Heck type reaction with an olefin as the first example of a C–C bond-forming reaction using silanols. For example, treatment of aromatic silanol **129** with iodobenzene in the presence of $Pd(PPh_3)_4$ as a catalyst and Ag_2O as an additive in tetrahydrofuran at 60 °C affords the coupling product **130** in 80% yield after 36 h (Scheme 2.11). Subsequently, Mori reported the usage of silandiol and silantriols in the cross-coupling reactions. [143]



129 **80%** **130**

Scheme 2.11: Pd-catalyzed Mizoroki-Heck type reaction of silanol **129** with PhI.

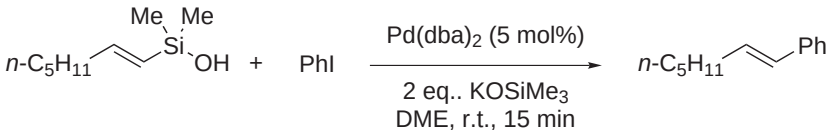
Subsequently, one year later, Denmark also demonstrated [144] the facility with which alkenylsilanols undergo the Pd-catalyzed cross-coupling reactions with aryl or vinyl iodides in the presence of tetrabutylammonium fluoride (TBAF) or tetrabutylammonium hydroxide. The advantages of Denmark's conditions over Mori's are that reactions can proceed at room temperature without the necessity for stoichiometric amounts of silver oxide and that the reaction proceed rapidly. As an example, alkenyl silanol **131** was reported to undergo Pd-catalyzed cross-coupling with iodobenzene in tetrahydrofuran in the presence of two equivalents of TBAF at room temperature and, after 10 min, olefin **132** was afforded in 82% yield with a very high *E/Z* ratio (99.2/0.8)(Scheme 2.12).



131 **91%** **132**

Scheme 2.12: Pd-catalyzed cross coupling of alkenyl silanol **131** with PhI.

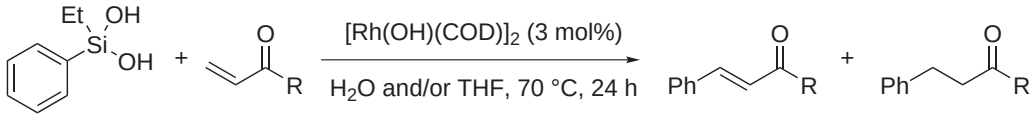
The use of the fluoride ion in such a complex molecule synthesis has several advantages, not least of which is the fact that it demonstrates a marked affinity for silicon (the Si–F bond is one of the shortest known bonds). Furthermore, TBAF is not inexpensive and, as such Denmark released an analog fluoride-free cross-coupling using stoichiometric amounts of base (rather than TBAF) the following year. This improved catalysis is demonstrated by the reaction of alkenyl silanol **131** with iodobenzene in DME at room temperature, which affords the olefin **132** after 15 min in 91% yield with a very high *E/Z* ratio (99.3/0.7) (Scheme 2.13).



131 **132**

Scheme 2.13: Fluoride free cross-coupling of alkenyl silanol **131** with PhI in the presence of base.

In 2001, Mori also reported [145] that the Rh-catalyzed reaction of silanediols with α,β-unsaturated esters can be directed toward either the Mizoroki-Heck (MH) type reaction or conjugate addition depending on the solvent system and the electronic nature of the carbonyl substrate. For example, the $[Rh(OH)(COD)]_2$ catalyzed reaction of silanediol **133** with acrolein (**134**) in tetrahydrofuran at 70 °C afforded conjugate addition product **136** in 56%, whereas the reaction of ethyl acrylate (**137**) under the same conditions afforded the product of MH-type reaction **138** in 74% yield, along with only trace amounts of conjugate adduct **139**. When water–THF (2:1) was instead used as a solvent mixture with this latter reaction systems, the conjugate adduct **139** was afforded as the main product in 53% yield along with a 5% yield of the product of MH-type reaction **138** (Scheme 2.14).

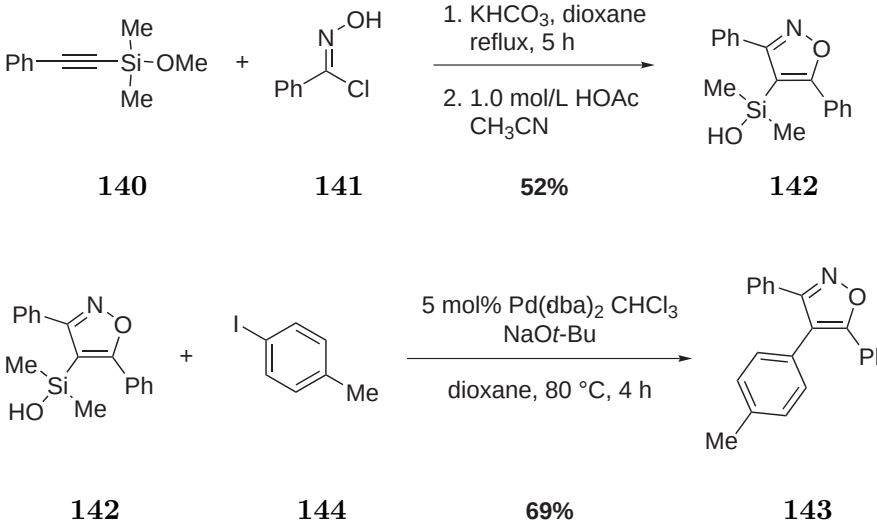


5 – 74% **0 – 53%**

133 **134** : R = Me **135** : R = Me **136** : R = Me
137 : R = OEt **138** : R = OEt **139** : R = OEt

Scheme 2.14: Rh-catalyzed Mizoroki-Heck type reaction and/or conjugate addition of silanols **133** with carbonyl substrate **134** and **137**.

In 2005, Denmark applied [146] his silanol-based cross-coupling reaction to the synthesis of 3,4,5-trisubstituted isoxazoles. A [3+2] cycloaddition reaction between silyl ether **140** and chlorooxime **141** afforded silanol **142** in 52% yield after hydrolysis. This silanol was subsequently subjected to a Pd-catalyzed cross-coupling reaction with 4-iodotoluene (**144**) at 80 °C in dioxane in the presence of 2.5 equivalents of KO*t*-Bu and 1 equivalent of $Cu(OAc)_2$, to afford 3,4,5-trisubstituted isoxazole **143** in 69% yield (Scheme 2.15).



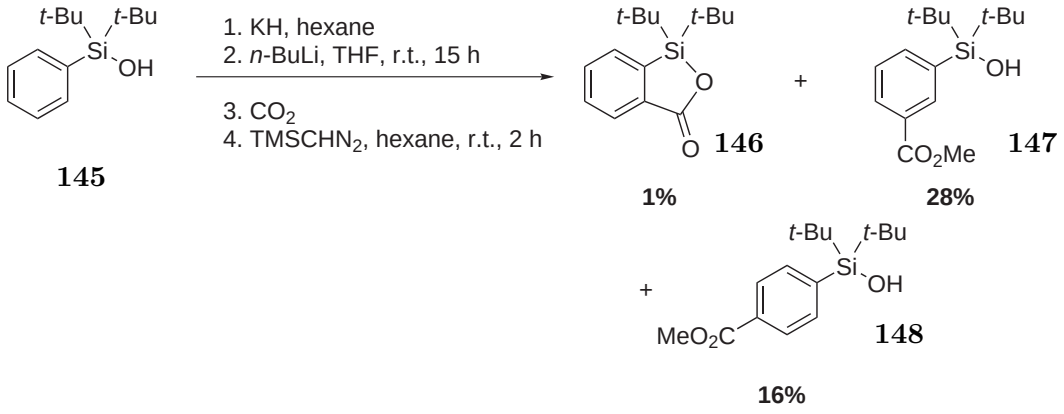
Scheme 2.15: The synthesis of tri-substituted isoxazole **143** *via* cross-coupling of silanol **142**.

2.3.2 The Silanol Moiety as a Directing Group

The directed *ortho*-metalation reaction is comprised of the deprotonation of an aromatic compound at a site that is located *ortho* to a heteroatom-containing directing group by a strong base, normally an alkyllithium reagent, leading to an *ortho*-metalated species. Silanols could be also used for this purpose, however, that the use of these compounds is only illustrated by the following example.

In 1993, Sieburth investigated [147] the possibility to use silanols as a new form of directing group for the *ortho*-metalation in aromatic compounds. However, rather than effecting solely *ortho*-metalation, the substituted aromatic products were observed as a mixture of isomers. For example, the treatment of silanol **145** first with KH in hexane, then with *n*-BuLi in THF at room temperature, followed by quenching with CO_2 and subsequent treatment with (trimethylsilyl)diazomethane, afforded several products, which were found to be the three carboxylated silanols **146**, **147** and **148**, which the first of resulted from intramolecular esterifica-

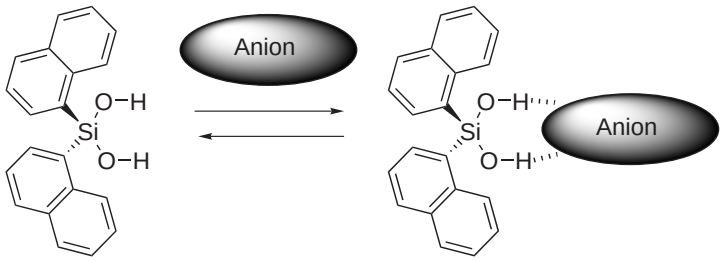
tion. Starting material was isolated in 42% yield. Although this method requires optimization, it demonstrates the application of silanols as directing groups in metalation reactions (Scheme 2.16).



Scheme 2.16: The utilization of silanol **145** as a directing group in aromatic metalation.

2.3.3 Silandiol-Based Anion Receptors

Very recently, Kondo demonstrated [148] the first example of silandiol as an anion receptor. As seen in Scheme 2.17, silanediol **149** is possible to be associated with anions such as chloride and acetate.



Scheme 2.17: Silanediol **149** as an anion receptor.

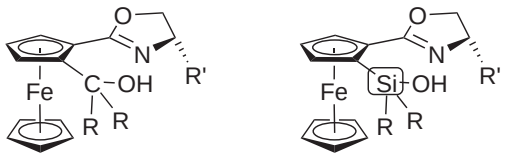
In order to discriminate whether the process is a hydrogen bond complexation or a proton transfer of a Bronsted-type acid-base equilibrium, they performed ^{1}H NMR dilution experiments of a 1:1 mixture of silanediol **149** and acetate, which resulted in a shift of CH protons of naphthyl groups to the direction of dissociation by dilution, which clearly showed that it is a hydrogen

bond complexation rather than the proton transfer.[5] Moreover, x-ray analysis of the complex of silanediol **149** with chloride, whereas tetrabutylammonium as a counterion, clearly indicated the hydrogen bond formation between chloride and hydrogen of Si–OH moieties.

2.4 Objectives of the Research

As presented in the introduction part, organosilanols have found important applications in various fields. Although it is not mentioned, they also play important roles in the production of silicon-based polymeric materials. [149] However, to the best of our knowledge, they have never been utilized as chiral ligands in catalytic asymmetric reactions.[6] Therefore, the application of silanols in asymmetric catalysis had caught our attention.

Recently, it was demonstrated that *ortho*-substituted ferrocene **150** with oxazolinyl- and diphenylhydroxy methyl groups is an effective catalyst for the asymmetric aryl transfer reaction to aldehydes leading to products with up to 99% ee. Motivated by these results, We wondered about the applicability of structurally analog organosilanols **153**, which have the same oxazolinyl-substituted ferrocene backbone, but differ in the hydroxyl-bearing side chain. The resulting steric and electronic modification was expected to have an impact on the examined catalyst system and alter its activity and selectivity.



150 **153**

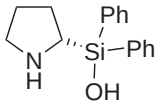
Figure 2.8: Carbinol **150** which is used as ligand in asymmetric aryl transfer reactions and its silanol analog **153**.

As the second part of the present work, application of organosilanols as directing groups on ferrocenes was explored. Having unexpected products from this study changed the direction of the project towards the synthesis of ferrocene-based silanediols and their application in hetero-Diels-Alder reaction.

[5] If the process would be a proton transfer, the equilibrium is independent of the concentration of the species, because the equilibrium constant is dimensionless.

[6] For examples of silanols in achiral metal complexes, see: [150] and references therein

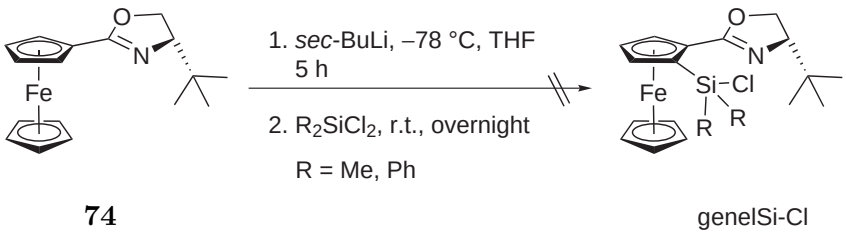
Enhanced acidity of silanols compared to carbon analog could be utilized in asymmetric catalysis in terms of increased reactivity. The synthesis and application of silicon analog of diphenylprolinol was the aim of the last project. The synthesis part is an ongoing project, which some of its preliminary results are briefly discussed.



2.5 Results and Discussion

2.5.1 Synthesis of Ferrocene-based Organosilanols

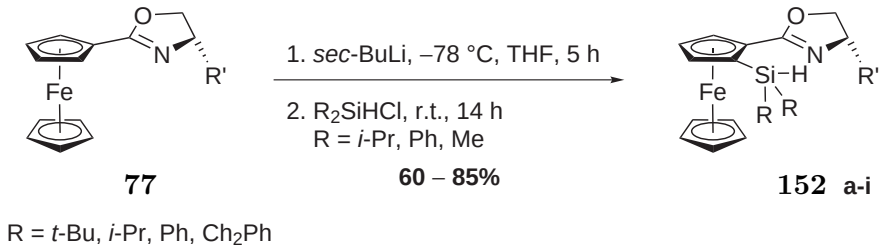
The first attempt for the synthesis of organosilanols using chlorosilane **151** as a key intermediate failed in the first step. Diastereoselective *ortho*-lithiations of ferrocenyl oxazolines **74**, with *sec*-BuLi at −78 °C in THF, followed by electrophilic attack with dichlorodimethyl silane gave only starting material. This might be due to the instability of chlorosilane moeity in the presence of oxazoline group which might react internally with Si–Cl bond and breaking the C–Si bond to form the starting material back. Ferrocenyl oxazolines **77** are readily available from ferrocene carboxylic acid following a known literature protocol. [151]



Scheme 2.18: Failed reaction of dimethyldichlorosilane in the synthesis of chlorosilan **151**.

Therefore, an alternative pathway has been tried in the synthesis of organosilanols **153**, using silanes **152** as key intermediates. A series of organosilanes has been prepared through following synthetic pathway. Diastereoselective *ortho*-lithiations of ferrocenyl oxazoline **77** with *sec*-BuLi at −78 °C in THF, followed by electrophilic attack with various chlorosilanes gave diastereomerically enriched 1,2-disubstituted ferrocenes **152** in good yields (60-85%) (Scheme 2.19) (Table 2.1). Since the diastereomers of silanes **152** were inseparable by simple flash chromatography, they have been used in the next step as diastereomeric mixtures. It has been also tried to prepare

organosilanes with *tert*-butyl groups at the silicon atom. Those attempts, however, remained unsuccessful, since lithiated oxazolines **77** did not react with di-*tert*-butylchlorosilane.

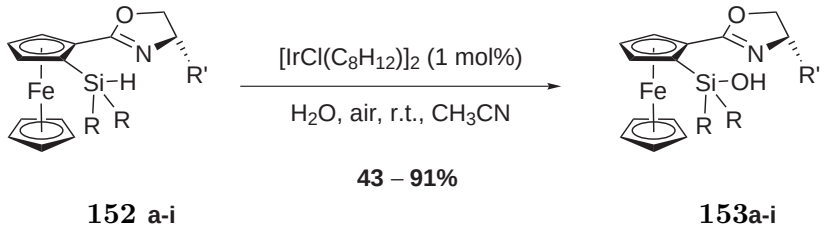


Scheme 2.19: Synthesis of organosilanes **152** *via ortho*-lithiation and subsequent quenching with electrophiles.

Table 2.1: Synthesis of organosilanes **152** *via ortho*-lithiation and subsequent quenching with chloro silanes.

Entry	Compound	R'	R	Yield (%)
1	**152a**	*t*-Bu	CH_3	64
2	**152b**	*t*-Bu	*i*-Pr	64
3	**152c**	*t*-Bu	Ph	91
4	**152d**	Ph	*i*-Pr	70
5	**152e**	Ph	Ph	68
6	**152f**	*i*-Pr	*i*-Pr	81
7	**152g**	*i*-Pr	Ph	85
8	**152h**	CH_2Ph	*i*-Pr	82
9	**152i**	CH_2Ph	Ph	60

Using a method recently introduced by Chang, [130] the silyl group of silanes **152** was oxidized in air with $[IrCl(C_8H_{12})]_2$ as catalyst giving ferrocenyl organosilanols **153**. After column chromatography and isolation of the major diastereomer, stereochemically homogeneous samples of organosilanols **153** were obtained in 43-91% yield (Scheme 2.20)(Table 2.2).



152 a-i **153a-i**

Scheme 2.20: Synthesis of organosilanols **153** *via* oxidation of Si–H bond with Ir catalyst.

Table 2.2: Synthesis of organosilanol **153** *via* oxidation of Si–H bond with Ir catalyst.

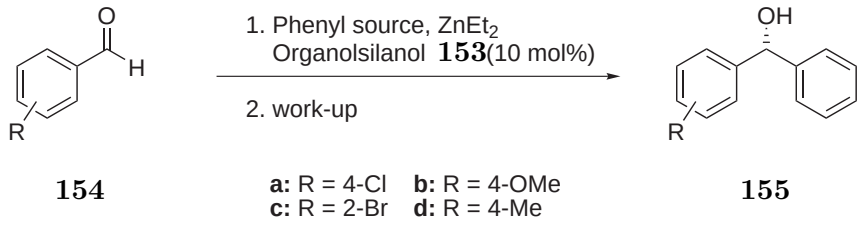
Entry	Compound	R'	R	Yield (%)
1	**153a**	*t*-Bu	CH_3	91
2	**153b**	*t*-Bu	*i*-Pr	75
3	**153c**	*t*-Bu	Ph	77
4	**153d**	Ph	*i*-Pr	57
5	**153e**	Ph	Ph	53
6	**153f**	*i*-Pr	*i*-Pr	65
7	**153g**	*i*-Pr	Ph	72
8	**153h**	CH_2Ph	*i*-Pr	45
9	**153i**	CH_2Ph	Ph	43

2.5.2 Application of Organosilanols in Asymmetric Reactions

The catalytic properties of organosilanols **153** were explored in asymmetric phenyl transfer reactions from organozinc reagents[7] to benzaldehydes **154** giving diarylmethanols **155**. The results are summarized in Table 2.3 in order to give the whole picture of the project.[8]

[7] A colloborations with Frank Schmidt had been done for this project. All reactions were run on a 0.25 mmol scale using 10 mol% of silanol **153**. Method A: use of Ph_2Zn (0.65 equiv) and Et_2Zn (1.3 equiv) in toluene at 10 °C for 12 h. Method B: use of Ph_3B (1.0 equiv) and Et_2Zn (3.0 equiv) at 10 °C for 12 h. Method C: use of $PhB(OH)_2$ (2.4 equiv) and Et_2Zn (7.2 equiv) and DiMPEG (10 mol%; MW = 2000 g/mol) in toluene (first at 60 °C for 12 h, then 10 °C for 12 h). Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product had *R* configuration

[8] For further details, please see Frank Schmidt's Dr. rer. nat. thesis. There results has been also published [152]



Scheme 2.21: Asymmetric phenyl transfer reaction to substituted benzaldehydes **154** using organosilanol-based catalysts and various zinc reagents.

Table 2.3: Asymmetric phenyl transfer reaction to substituted benzaldehydes **154** using organosilanol-based catalysts and various zinc reagents.

Entry	Substrate	Organosilanol	Method (Product)	Yield (%)	e.e.(%)
1	**154a**	**153a**	A (**155a**)	40	30
2	**154a**	**153b**	A (**155a**)	82	91
3	**154a**	**153c**	A (**155a**)	84	89
4	**154a**	**153d**	A (**155a**)	82	87
5	**154a**	**153e**	A (**155a**)	76	85
6	**154a**	**153f**	A (**155a**)	87	78
7	**154a**	**153g**	A (**155a**)	73	76
8	**154a**	**153h**	A (**155a**)	85	63
9	**154a**	**153i**	A (**155a**)	nd[9]	58
10	**154a**	**153c**	B (**155a**)	73	88
11	**154a**	**153c**	C (**155a**)	67	83
12	**154b**	**153c**	A (**155b**)	81	87
13	**154c**	**153c**	A (**155c**)	70	84
14	**154d**	**153c**	A (**155d**)	84	83

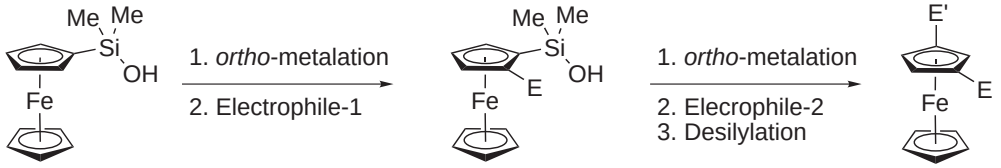
Although the observed enantioselecitivities are slightly lower than those of the corresponding carbinols, [153–155] the method certainly demonstrates a possibility to use silanols as a ligand for enantioselective metal catalysts.

As a result, the use of silanols in catalysis has promising prospectives as analog to carbon-

based alcohols, due to changes in bond length, proton acidity and atomic radius.

2.5.3 Organosilanols as Directing Group on Ferrocenes

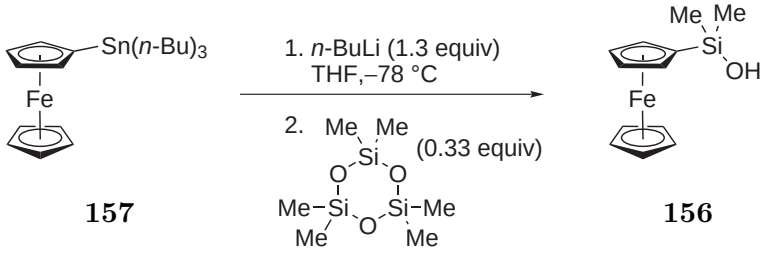
Inspired by the work of Sieburth, summarized in Scheme 2.16, silanols could be used as a directing group in ferrocenes. Since the removal of silanols could be relatively easy, double functionalization of *ortho*-position of silanols was aimed for the synthesis of 1,3-disubstituted ferrocenes (Scheme 2.22).



156

Scheme 2.22: Utilization of silanol **156** in the synthesis of 1,3-disubstituted ferrocenes.

Dimethylferrocenylsilanol **156** could be synthesized in one step starting from ferrocenyl tin compound **157** which is readily available from ferrocene following known literature protocols (Scheme 2.23). [156][10] Interestingly, using one equivalent of hexamethyltrisiloxane did not afford the desired product **156** at all.



157 **156**

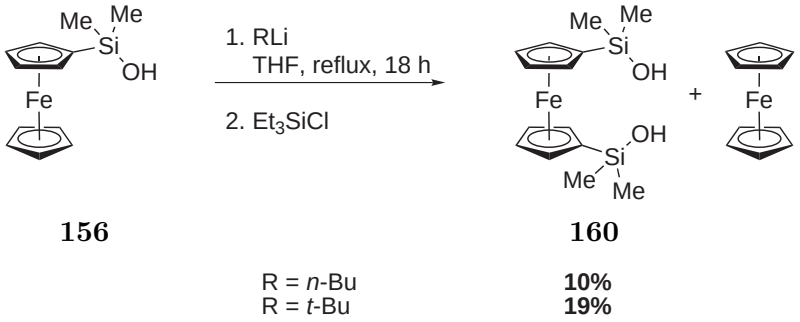
44%

Scheme 2.23: Synthesis of silanol **156** from ferrocenyl tin **157**.

Following a modified procedure of Sieburth [147] for the metalation reaction, silanol **156** has been treated with *n*-BuLi, refluxed in THF and quenched with Et_3SiCl. After work up, beside starting material, unexpected products **160** were obtained in poor yield. Changing the lithium

[10] An alternative synthesis could be done in two-step using dimethylchlorosilane and subsequent oxidation of Si–H to Si–OH, but one-step synthesis was prefered due to higher yields.

species to *tert*-BuLi afforded the same product **160** with a better yield.

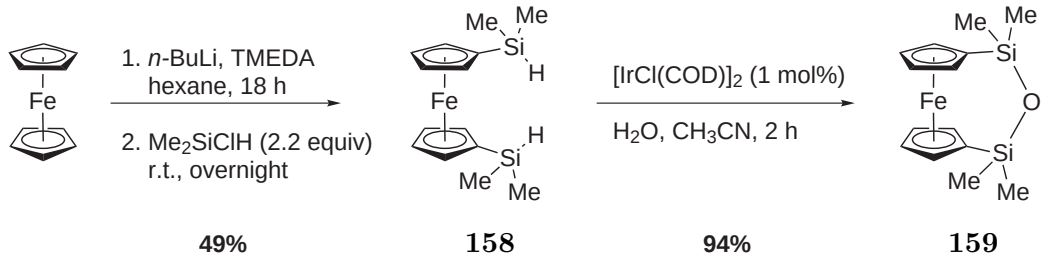


Scheme 2.24: Unexpected result after *ortho*-lithiation of silanol **156**.

This results showed that instead of *ortho*-lithiation, 1'-lithiation occured and intramolecular reaction furnished disilanol **160** and ferrocene.

2.5.4 Synthesis of Ferrocene-Based Disilanols

Although the desired synthetic method for the synthesis of 1,3-disubstituted ferrocenes had failed, disilanol **160** has caught attention for further studies. Disilanol could be used as a ligand or organocatalyst for many reactions. For that reason, the synthesis of disilanol has been tried starting from ferrocene. The formation of 1,1'-lithiated ferrocene with *n*-BuLi and TMEDA and quenching with dimethylchlorosilane afforded the corresponding disilane **158** in 27% yield (Scheme 2.25). However, the oxidation of disilane with Ir-catalyst did not afford the desired product but a cyclized disilanol **159** (a siloxane).

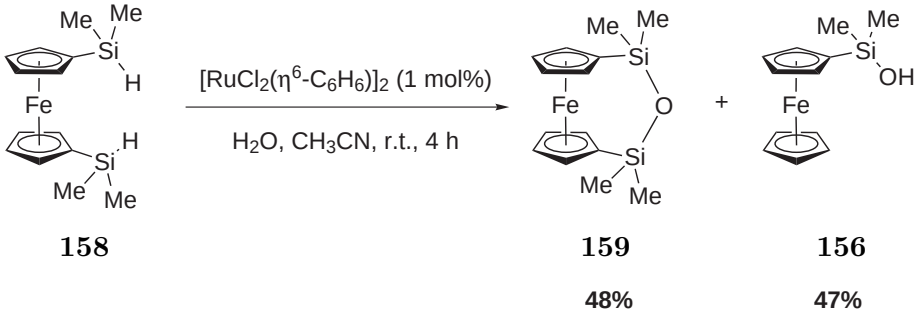


Scheme 2.25: Unsuccesful attempt through the synthesis of disilanol **160** with an Ir-catalyst.

There are two possible pathways for the formation of this unexpected product **159**. The first one is that, under reaction conditions, disilanols **160**, cyclized to give siloxane **159**. The second possibility is that after the oxidation of one Si–H bond, the oxidation of second Si–H

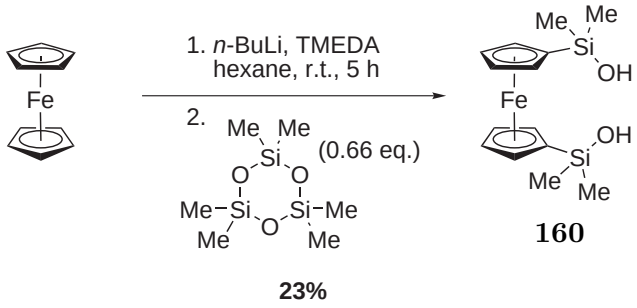
bond occurs by means of Si–OH moiety by intermolecular reaction, rather than water.

Using $[RuCl_2(\eta^6\text{-benzene})]_2$ as catalyst for the oxidation, gave the same siloxane and monosilanol in good yields (Scheme 2.26). The formation of monosilanol **156** could not be understood without a knowledge of the mechanism.



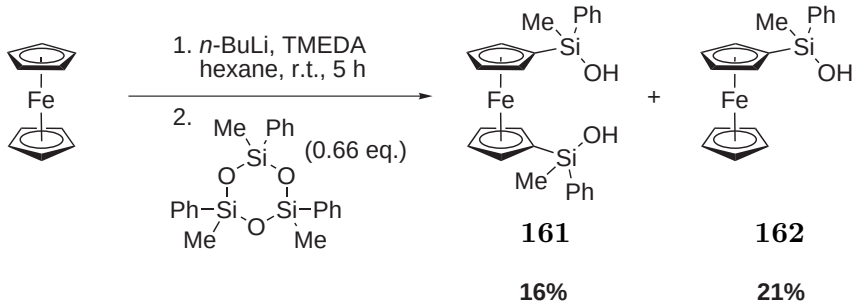
Scheme 2.26: Unsuccesful attempt through the synthesis of disilanol **160** with a Ru-catalyst.

Nevertheless, instead of searching for alternative oxidation methods, the synthetic pathway was changed to one-step procedure as for in the synthesis of silanol **156**. For this purpose, 1,1'-lithiated ferrocene was quenched with hexamethyltrisiloxane to afford the desired disilanol **160** in 23% yield (Scheme 2.27).



Scheme 2.27: One-pot synthesis of disilanol **160**.

Since 1,1'-disubstituted ferrocenes are achiral, in order to synthesize a chiral version of disilanol, 1,1'-dilithiated ferrocene has been reacted with 1,3,5-trimethyl-1,3,5-triphenyl-trisiloxane to give a mixture of racemic and meso form of disilanol **161** and monosilanol **162** as a side-product (Scheme 2.28).

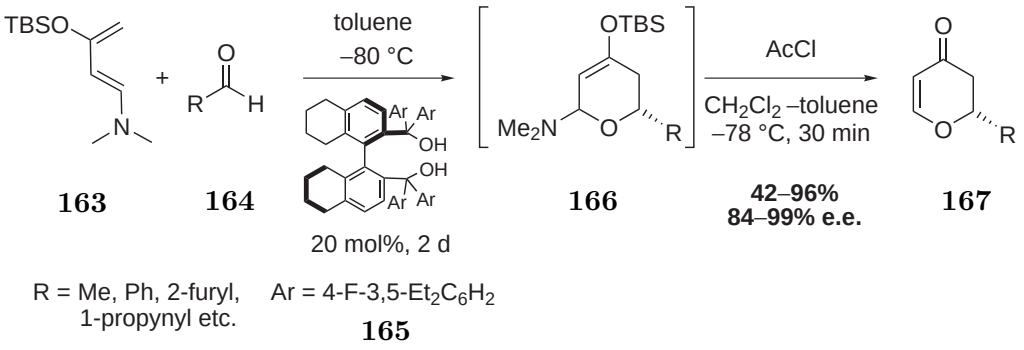


Scheme 2.28: Synthesis of disilanol **161**.

Racemic and meso mixture of disilanols **161** were separated by preparative HPLC using chiral stationary columns. However, in agreement with Tacke's results [120], chiral silicon center of disilanol **161** can easily racemize in the presence of water and alcohol. Since an *iso*-propanol-hexane mixture was used as an eluent in the preparative HPLC, after separation and removal of the solvent, disilanol **161** was found to be already epimerized in the solution.

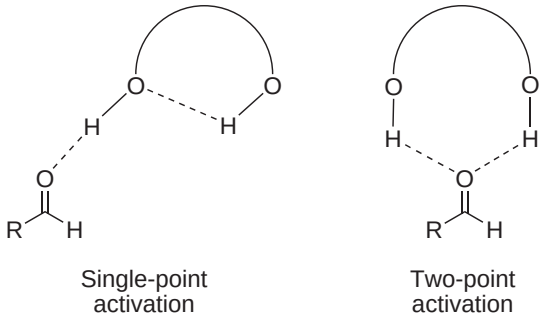
2.5.5 Hydrogen Bond Catalyzed Hetero-Diels-Alder Reaction

Recently, Rawal and Yamamoto [157,158] showed a highly enantioselective hetero-Diels-Alder (HDA) reaction using chiral diols as catalysts. This was one of the major breakthrough in hydrogen bond catalyzed reactions. Chiral diols were acting as a Lewis acid by activating the carbonyl group of the aldehyde through double hydrogen bonding. For example, he reported that diene **163** could undergo a hetero-Diels-Alder reaction with aryl aldehyde **164** at −80 °C in toluene and BAMOL **165** as catalyst to afford the intermediate **164** which could be converted to 1,2-dihydropyran **164** upon reacting with acetylchloride at −78 °C in CH_2Cl_2-toluene for 30 min (Scheme 2.29).



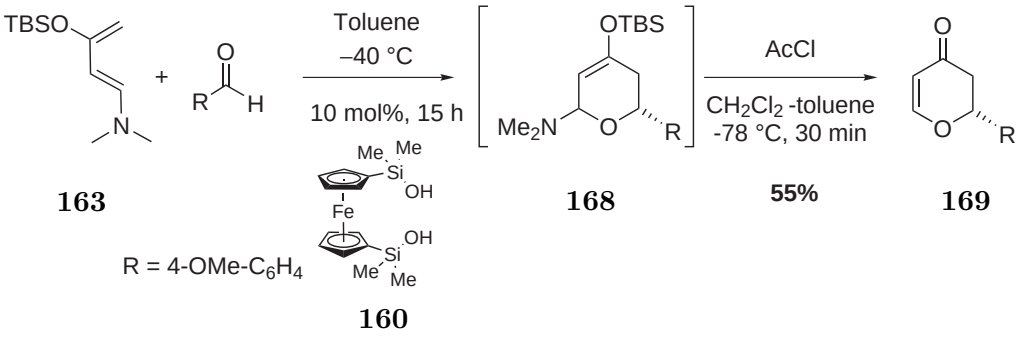
Scheme 2.29: Hydrogen bond catalyzed Hetero-Diels-Alder reaction of Rawal and Yamamoto.

X-ray structure analysis of the complex of 2,2'-bis-(diphenylhydroxymethyl)binaphthylene (as a simple family of BAMOL **165**) with benzaldehyde showed that there is an intramolecular hydrogen bond between two hydroxyls and an intermolecular hydrogen bond to the carbonyl oxygen of benzaldehyde. [158] This indicates that the reaction was probably catalyzed through the single-point rather than two-point activation (Scheme 2.30).



Scheme 2.30: The possible mechanism of hydrogen bond activation of aldehydes.

Taking into account the higher acidity of silanols compared to that of carbon analog, disilanol **160** was selected to be tested as an organocatalyst in hydrogen bond catalyzed HDA reaction following the Rawal's procedure and moderate activity was observed. Since, an enantiopure disilanol could not be isolated, the enantioselective version of HDA was not possible to test. [11]



Scheme 2.31: Disilanol **160** catalyzed hetero-Diels-Alder reaction.

[11] Christine Beemelmans performed a kinetic study using reactIR in which the ratio of the HDA reaction, when catalyzed by disilanol **160** was found to be comparable with that obtained when the structurally analogous paracyclophanyl disilanols were used as catalysts. For further details, see: Beemelman's Diploma Thesis, RWTH – Aachen University, 2006.

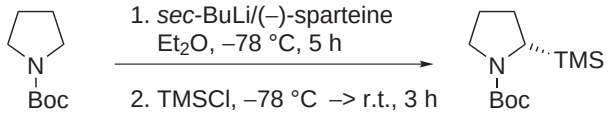
2.5.6 On the Way to a Silanol Analog of Prolinols

(*S*)-Diphenylprolinol (**170**) is a well known amino alcohol that has found many applications in asymmetric catalysis. For example, it is the precursor of a series of chiral oxazoborolidines known as CBS-catalyst which is particularly used in the reduction of carbonyl compounds [159] beside many other reactions such as Diels-Alder [160] or Michael reactions. [161]

170 **171**

Figure 2.9: Prolinol **170** and sila-prolinol **171**.

Enhanced acidity of silanols compared to carbon analogs could be utilized in asymmetric catalysis in terms of increased reactivity. The silicon analog of diphenylprolinol (Figure 2.9) was aimed to be synthesized via (–)-sparteine assisted asymmetric lithiation[12] of *N*-Boc-pyrrolidine. [164, 165] It is a method which was initially introduced by Beak [164]and further developed by many other groups.[13] For example, *N*-Boc-pyrrolidine (**172**) could be enantioselectively deprotonated with (–)-sparteine/*sec*-BuLi system and quenched with TMSCl to afford pyrrolidine **172** in good yield and high enantioselectivity (Scheme 2.32).



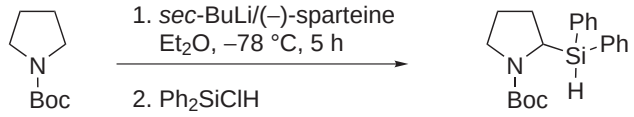
172 **71%** **94% e.e.** **173**

Scheme 2.32: (–)-Spartein assisted asymmetric functionalization of *N*-Boc-pyrrolidine with TMSCl.

Using this well-known method, the synthesis of sila-prolinol **171** became a target of the project. Initially, in order to established a suitable synthetic method, the racemic synthesis of desired silanol **171** was tested using achiral amine such as *N,N,N',N'*-tetrametylethylenediamine (TMEDA) but deprotonation of *N*-Boc-pyrrolidine (**172**) could not be achieved. Therefore,

[12] For review about enantioselective synthesis with lithium/(–)-spartein carbanion pairs: see refs. [162] and [163]
[13] For representative examples: see ref. [165–168]

it was decided to perform the enantioselective synthesis using (–)-sparteine. Enantioselective deprotonation of *N*-Boc-pyrrolidine with (–)-sparteine/*sec*-BuLi, and subsequent treatment with hexaphenyltrisiloxane did not afford the desired *N*-Boc-silane **174**. When diphenylchlorosilane was used instead of using hexaphenyltrisiloxane, reaction proceeded well and gave the desired silane **174** in moderate yield. Enantiomeric excess of the product could not be determined yet.

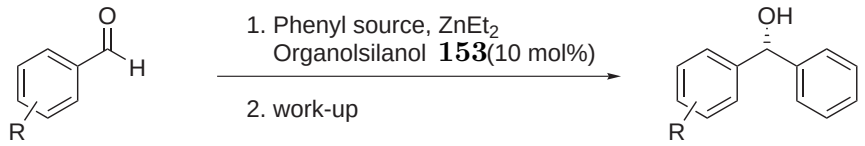


172 **60%** **174**

Scheme 2.33: (–)-Spartein assisted asymmetric functionalization of *N*-Boc-pyrrolidine with diphenylchlorosilane.

2.6 Summary and Outlook

In the present chapter, the synthesis of planar-chiral ferrocene-based organosilanols **153** was described. High enantioselectivities and yields of up to 91 and 87%, respectively, have been achieved in a colloboration with Frank Schmidt using both zinc and boron-based aryl sources. Although silanols **153** gave lower yields and enantiomeric excesses compared to carbinol analog **150**, to the best of our knowledge this is the first application of chiral organosilanols in asymmetric catalysis (Scheme 2.34).



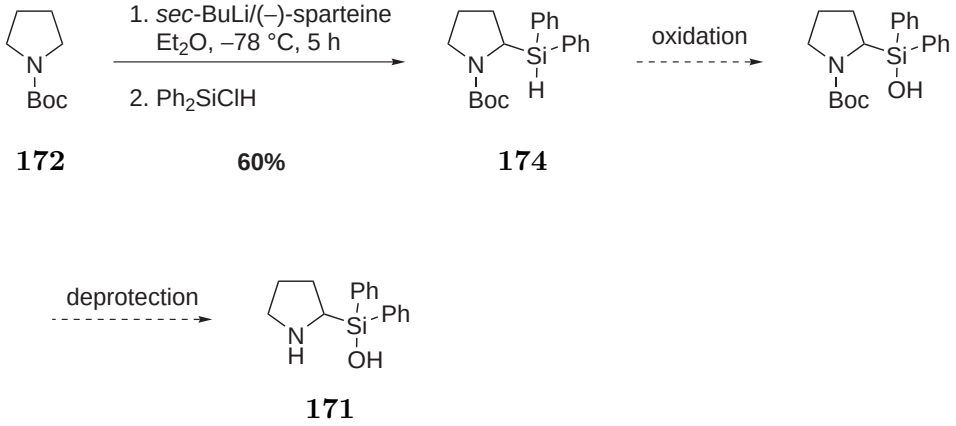
154 **a:** R = 4-Cl **b:** R = 4-OMe **c:** R = 2-Br **d:** R = 4-Me **155**

Scheme 2.34: Asymmetric phenyl transfer reaction to substituted benzaldehydes **154** using organosilanol-based catalysts and various zinc reagents.

Application of silanols as directing group on ferrocenes is still an ongoing project. They can be further investigated for their utilization as the directing group to 1'-position on ferrocenes. Synthesis of a disilanol having a chiral silicon atom was tried, however, due to the racemization

in the alcoholic solution, no optically active silanol was obtained. Achiral disilanol **160** was tested as organocatalyst in a hetero-Diels-Alder reaction and moderate activity was observed.

On this work, although the synthesis of sila-prolinol **171** could not be completed, the preliminary result towards the synthesis of it was presented.



Scheme 2.35: Outlook and future plan for the synthesis of sila-prolinol **171**.

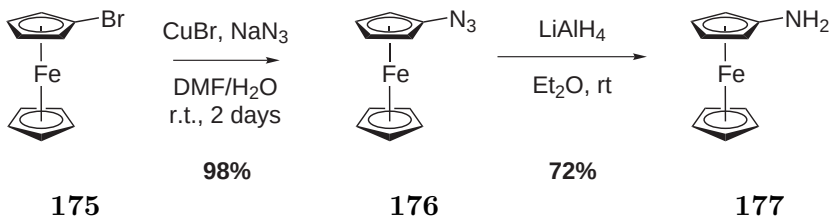
Chapter 3

N-Substituted Ferrocene Derivatives

Following the discovery of the ferrocenes in the 1950's, [169, 170] over the decades, ferrocene and its derivatives have been in the focus of a large number of investigations, that have revealed an enormous potential for the use of such materials in applied organometallic chemistry [171] and material science. [172] The interest in ferrocenes stems largely from the fact that although these organometallics are classical aromatic compounds, they can have rather unique properties due to their particular electronic and geometric features. As a consequence, standard methods for the functionalization of aromatic compound often prove unsuitable for the synthesis and modification of ferrocene derivatives and, hence, novel approaches to the formation of compounds such as ferrocenyl amines have been, and actually, are being, developed.

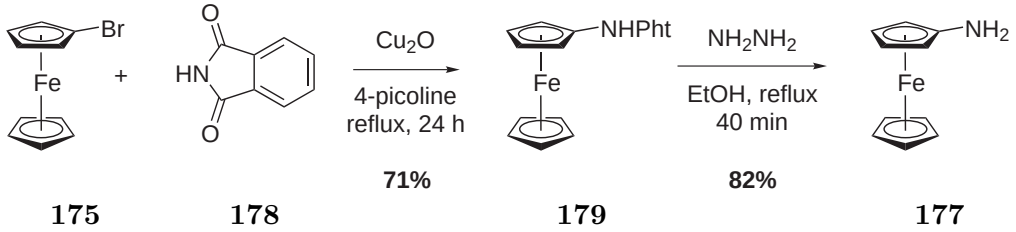
3.1 Syntheses of Ferrocenyl Amine

The synthesis of ferrocenyl amine (**177**) was first achieved by Nesmeyanov in 1955 by the reaction of *O*-derivative of hydroxylamine with ferrocenelithium. [173] In 1963, Nesmeyanov published [174] a second, improved protocol for the preparation of ferrocenyl amine (**177**) by the reduction of ferrocenyl azide (**176**). As shown in Scheme 3.1 ferrocenyl azide (**176**) was synthesized in very high yield (98%) by the reaction of bromoferrocene with sodium azide in the presence of CuBr in DMF/H_2O, in the dark, at room temperature for 2 days. Upon reduction of azide **176** with $LiAlH_4$ in diethyl ether, ferrocenyl amine was obtained in 72% yield.



Scheme 3.1: Nesmeyanov's two-step synthesis of ferrocenyl amine (**177**) by copper mediated sodium azide coupling and subsequent reduction with $LiAlH_4$.

In 1981, Sato reported [175] that copper(I) oxide in pyridine was an effective promotor for the initial nucleophilic substitution step in a modified Ullmann coupling to furnish ferrocenyl amine (**177**) after reflux with hydrazine. Specifically, bromoferrocene (**175**) reacts with phthalimide (**178**) in the presence of Cu_2O in 4-picoline to afford *N*-ferrocenyl phthalimide (**179**) in 71% yield after 24 hours at reflux. Phthalimide **179** was reduced to afford ferrocenyl amine (**177**) in good yield (82%) upon treatment with hydrazine in ethanol when held under reflux conditions for 40 minutes (Scheme 3.2).[1]



Scheme 3.2: Cu(I)-mediated condensation of bromoferrocene with phthalimide by Sato

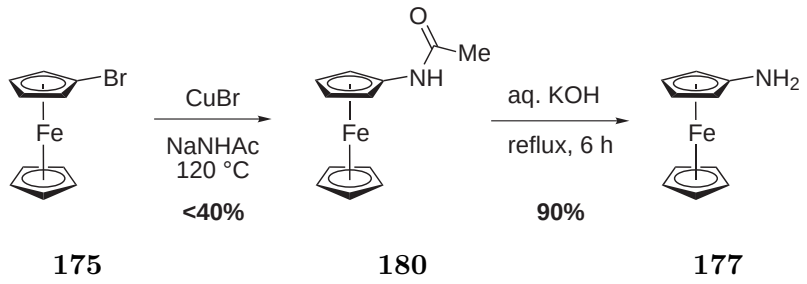
In 1999, Bildstein reported [177,178] an optimized, high-yielding version of this synthesis for the large scale (≤20 g) preparation of ferrocenyl amine (**177**) from ferrocene and, later applied this method to the synthesis of *N,N*-diferrocenyl-*N*-heterocyclic carbenes.

The discovery by Herberhold [179] in 1983, shows that ferrocenyl amine (**177**) can be obtained from ferrocenyl bromide (**175**) with sodium amides in the presence of copper(I) bromide. This two-step procedure, described in Scheme 3.3, involves the reaction between bromo ferrocene (**175**) and the sodium salt of acetamide in the presence of CuBr at 120 °C to afford *N*-ferrocenyl acetamide (**180**) in less than 40% yield in addition to 1,1-biferrocene as a side product.[2] Hydrolysis of amide **180** in refluxing aquoues KOH gave ferrocenyl amine (**177**) in 90% yield (Scheme

[1]The reduction step has been previously described by Nesmeyanov [176]

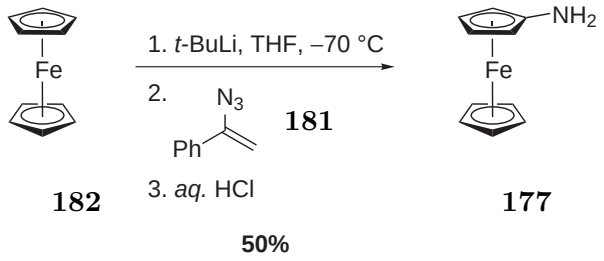
[2]The procedure was adapted from early work of Nesmeyanov. See: [180]

3.3).



Scheme 3.3: Herberhold's method of the synthesis of ferrocenyl amine (**177**).

Recently, Hessen reported [181] a synthesis which is adapted from an early work of Hassner [182] for the synthesis of anilines and heteroaromatic amines, using α-azidostyrene (**181**) as a nitrogen source. As shown in Scheme 3.4, ferrocene was lithiated with *t*-BuLi in tetrahydrofuran, and the resulting reaction mixture was subsequently reacted with α-azidostyrene (**181**) at -70 °C, prior to being subjected to acidic work-up, to afford ferrocenyl amine (**177**) in 50% yield. The disadvantage of this method is that it involves the use of an azide **181**[3] which can be dangereous for macro-scale synthesis of ferrocenyl amine (**177**).



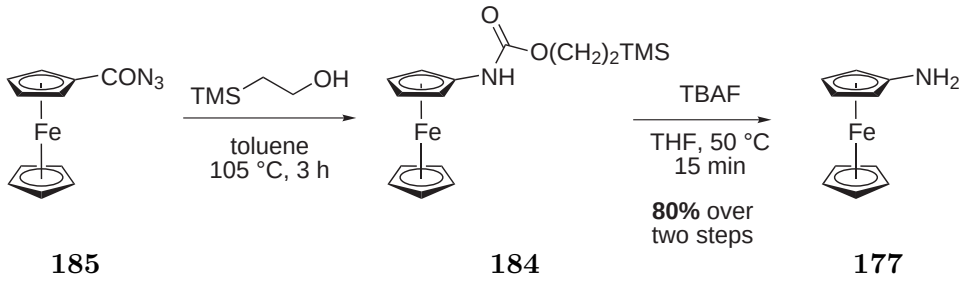
Scheme 3.4: Hessen's synthesis of ferrocenyl amine (**177**) *via* the reaction of lithiated ferrocene with azidostyrene.

In 2002, Richards provided [184] an alternative method for the formation of ferrocenyl amine (**177**) using an optimized version of the synthesis reported by Arimoto [185] in which the amine moiety was installed *via* Curtius rearrangement. Azide **183**[4] undergoes Curtius rearrangement upon heating to 105 °C and, in the presence of 2-trimethylsilylethanol, the resulting isocyanate

[3] For its synthesis from styrene in three steps, see: [183]

[4] Ferrocene carboxylic azide can be easily synthesized from ferrocene carboxylic acid through one-pot two-step synthesis. [184]

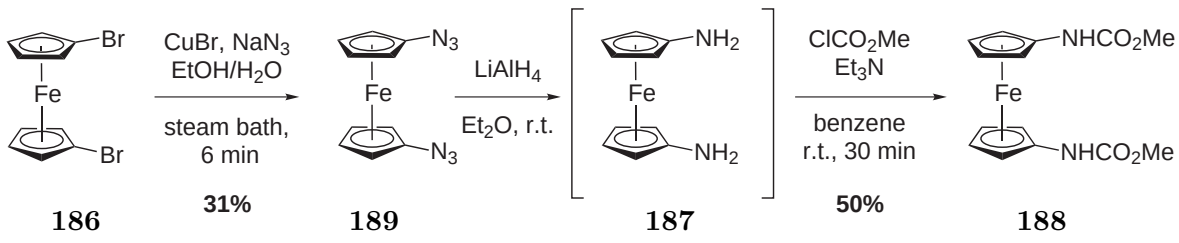
reacts to afford the corresponding carbamate **184** which can be deprotected on treatment with excess TBAF to furnish ferrocenyl amine (**177**) in 80% overall yield (Scheme 3.5).[5]



Scheme 3.5: Richard's synthesis of ferrocenyl amine (**177**) *via* Curtius rearrangement.

3.2 Synthesis of 1,1'-Diamino Ferrocene

1,1'-Diamino ferrocene has been synthesized and converted into corresponding carbamate derivative by Nesmeyanov [174] but could not be isolated due to its propensity to oxidize in air. As shown in Scheme 3.6, an ethanolic solution of 1,1'-dibromo ferrocene (**186**) was treated with aqeuous solution of sodium azide in the presence of CuBr on a steam-bath for 6 minutes to afford 1,1'-diazido ferrocene (**189**) in 31% yield. $LiAlH_4$ reduction of diazide **189** in dry diethyl ether gave diamine **187** which was immediately converted to carbamate **188** upon treatment with methylchloroformate, in the presence of triethylamine in 50% yield.



Scheme 3.6: Nesmeyanov's two-step synthesis of 1,1'-diamino ferrocene(**187**) *via* copper mediated sodium azide coupling and subsequent reduction with $LiAlH_4$.

For a long time, the synthesis of 1,1'-diamino ferrocene (**187**) was not further examined until a report by Arnold [188] about an improved high-yield synthesis of 1,1'-diamino ferrocene (**187**)

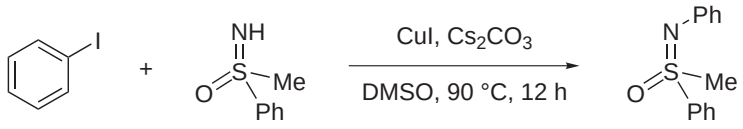
[5]Togni [186] and Shabat [187] also reported the synthesis of ferrocenyl amine (**177**) *via* similar method with small modifications.

via modified Nesmeyanov synthesis. Arnold showed that when the same reaction was performed over 48 hours at room temperature using CuCl (instead of the conditions specified above) in the initial step of the Nesmeyenov sequence, the yield of 1,1'-diazido ferrocene (**189**) could be improved to 59%. The reduction of diazide **189** with H_2/Pd in methanol (instead of $LiAlH_4$ in diethyl ether) provided 1,1'-diamino ferrocene (**187**) as a yellow crystalline substance after 6 h.

3.3 Objectives of the Research

Presumably due to synthetic problems, nitrogen-substituted ferrocenes are relatively unexplored. The most common way for their preparation is the derivatization of amino- (Fc-NH_2) and diaminoferrocene which are readily available by several well-established synthetic routes some of them being described in the introduction part. This dependence of the synthesis different *N*-substituted ferrocenes from ferrocenyl amine (**177**), restrains the diversity of the synthesis these type of compounds. For this purpose, we were interested in a general synthesis of *N*-substituted ferrocenes, especially, through C–N bond formation.

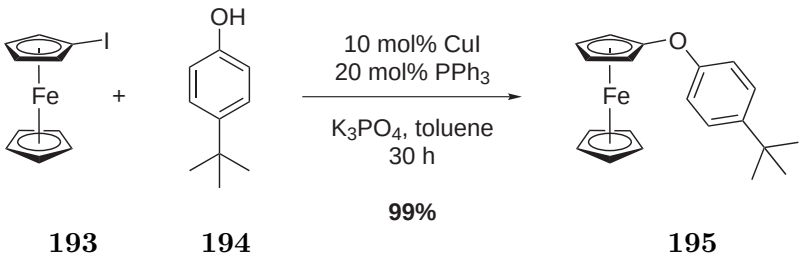
Recently, Bolm developed [189] the copper(I) iodide catalyzed cross-coupling reactions affording *N*-arylated sulfoximines in high yields. This approach represented an alternative method for the well-established palladium-catalyzed coupling reaction. For example, *N*-arylation of sulfoximine **191** with phenyl iodide **190** as an aryl source and Cs_2CO_3 as a base, in the presence of CuI at 90 °C in DMSO, afforded *N*-phenyl sulfoximine **192** in high yield (Scheme 3.7). Catalytic version of this reaction was also published by Bolm. [190, 191]



190 **191** **191**

Scheme 3.7: CuI-mediated phenylation of sulfoximine **191** by Bolm.

The same copper salt was used in catalytic amount by Plenio, [192] who prepared ferrocenyl aryl ethers in good yields starting from iodoferrocene. For example, ferrocenyl aryl ether **195** could be synthesized in high yield by CuI/PPh_3 catalyzed coupling reaction from iodoferrocene (**193**) and phenol **194** (Scheme 3.8).



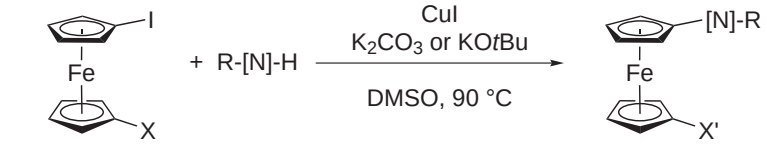
193 **194** **195**

Scheme 3.8: Cu-catalyzed synthesis of ferrocenyl aryl ether **195** by Plenio.

3.4 Results and Discussions

3.4.1 A General Synthesis of Ferrocenyl Amines

In the light of the results mentioned above, iodoferrocene or 1,1'-diiodoferrocene was chosen as coupling component in combination with cheap and readily available copper(I) iodide for the development of a direct synthesis of *N*-substituted ferrocenes by C–N cross-coupling.



193 X = H
196 X = I

X' = H, [N]-R

Scheme 3.9: General synthesis of *N*-substituted ferrocenes

The reactions were performed at 0 °C using DMSO as solvent and K_2CO_3 or KO*t*-Bu as base. Different solvents such as DMF or CH_3CN were also tested but they did not improve the yields. Using other carbonate bases than K_2CO_3 such as Cs_2CO_3 or Na_2CO_3 also did not have any positive effect on the yield of the reaction.

Generally, less nucleophilic nitrogen derivatives having electron-withdrawing groups gave the best results. For example, high yields were obtained in couplings with methyl phenyl sulfoximine (**191**), pyrazole and its chiral derivative **197**. Since ferrocenyl is an electron rich group, when nitrogen is directly attached to the ferrocene, it becomes very electron rich and reactive. Therefore, electron-withdrawing groups on nitrogen are mostly required in order to to obtain high stability of the products. There is a rough correlation between the pK_b of Fc-N-H and the yield of its product. Yields are increasing when nitrogen compounds are possesing higher pK_b

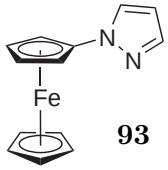
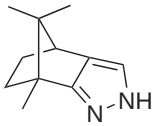
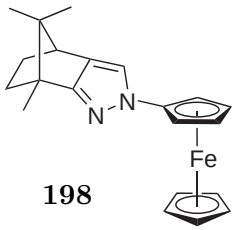
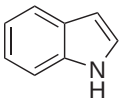
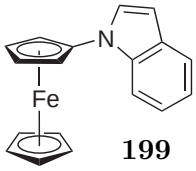
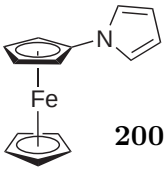
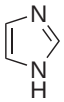
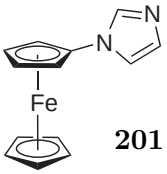
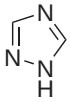
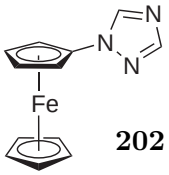
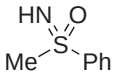
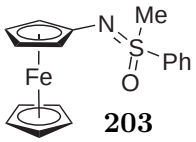
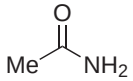
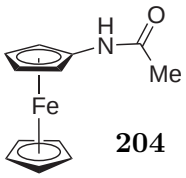
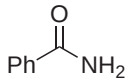
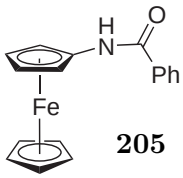
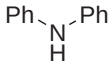
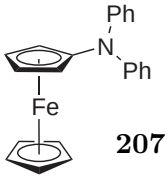
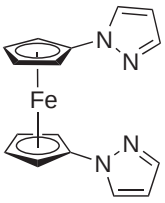
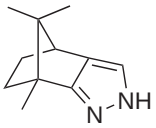
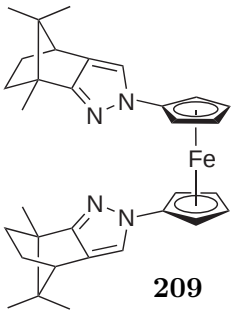
Entry	Coupling Component	Product	Yield (%)
1		 **93**	84
2	 **197**	 **198**	70
3		 **199**	73
4		 **200**	62
5		 **201**	31
6		 **202**	30
7		 **203**	80
8		 **204**	70

Table 3.1: Products of the coupling of iodoferocene (**193**) and 1-1'-diiodoferrocene (**196**) with coupling components.

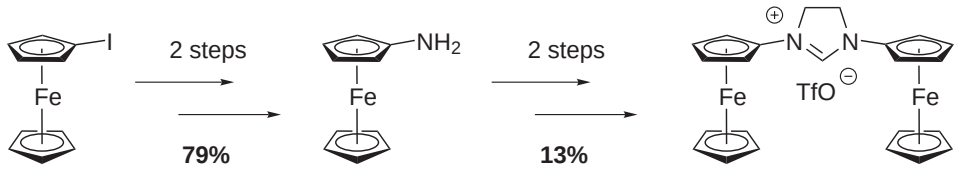
(contn'd Table 3.4.1)

Entry	Coupling Component	Product	Yield (%)
9		 **205**	57
10		 **207**	43
11		 **208**	50
12	 **197**	 **209**	31

values. This could imply that the rate determining step of the reaction is the removal of the hydrogen attached to nitrogen with a base and as a result of this nitrogen compound having low pK_b do not react or react with low yields and forming relatively less stable products. This may also explain why aniline and diphenylamine resulted in only poor conversions and low yields and, aliphatic amines such as morpholine, *n*-butyl amine and diphenylprolinol (**170**) did not react at all.

On the other hand, unexpected lower yielding reaction of imidazole and triazole could not be accounted for these explanations. This shows that reactivity of nitrogen compounds could be also dependent on the stereoelectronic properties of other intermediates in the reaction.

Although reactions with imidazole and triazole gave lower yields, they were of synthetic interest, since they led to products such as imidazole **201** and triazole **202**, which could be valuable compounds in *N*-heterocyclic carbene chemistry. Similar ferrocenes were commonly prepared by derivatization of ferrocenyl amine (**177**) over several steps. For example, Bildstein [177] has synthesized *N,N'*-diferrocenyl-*N*-heterocyclic carbene precursor **210** starting from iodoferrocene (**193**) over 4 steps and around 10% overall yield (Scheme 3.10).

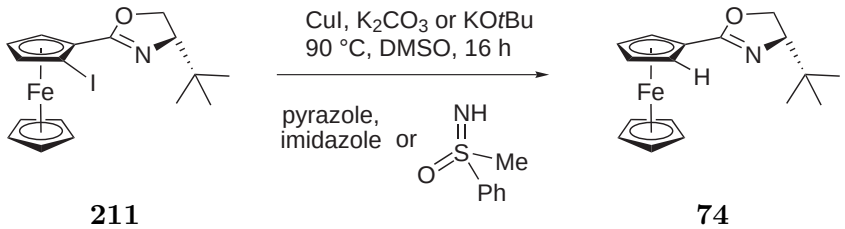


193 **177** **210**

Scheme 3.10: Bildstein's synthesis of *N,N'*-diferrocenyl-*N*-heterocyclic carbene precursor **210** starting from iodoferrocene (**193**).

The coupling of amides such as acetamide and benzamide required the use of the stronger base KO*t*-Bu to achieve better yields. Surprisingly, *N*-Cbz-proline amide did not afford the desired chiral ferrocene derivative even in the presence of KO*t*-Bu. Acetylhydrazide was also tested in the coupling with iodoferrocene (**193**), however, it did not afford the desired product.

The coupling of *o*-iodo-ferrocenyl oxazoline **211** with either pyrazole or methyl phenyl sulfoximine (**191**) produced only deiodinated product **74**. This can be attributed to steric crowdening and a negative effect of another coordination site for the metal, which is also consistent with the low yield of the bis-coupling products (Scheme 3.11).



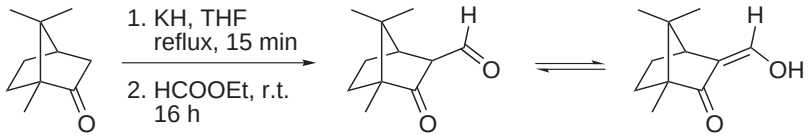
211 **191** **74**

Scheme 3.11: Copper-mediated coupling of iodooxazoline **211** with sulfoximine **191** or pyrazole or imidazole.

Double cross-couplings using 1,1'-diiodoferrocene were only successful with pyrazole deriva-

tives. The low yields were due to the formation of mono-coupling and mono-deiodination by-products. The attempt to use methyl phenyl sulfoximine led to a mixture of bis- and mono-coupled product together with the mono-coupled/mono-deiodinated ferrocene in low yield. Amides such as acetamide and *N*-Cbz-prolinamide did not react.

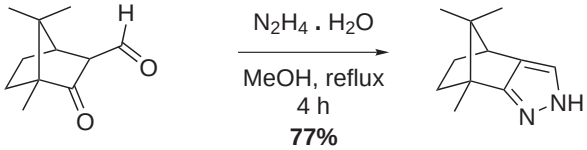
Chiral pyrazole was prepared from (+)-camphor (**212**) following a known literature protocol through a two-step synthesis. (+)-Camphor (**212**) was first refluxed with excess amount of KH[6] in THF for 15 min, quenched with ethyl formate and stirred at room temperature overnight to give α-carbaldehyde keton **213**[7] in moderate yields (Scheme 3.12).



212 **213** **214**

Scheme 3.12: The first step in the synthesis of chiral pyrazole **197**.

In the second step, α-carbaldehyde keton **213** was treated with hydrazine hydrate and refluxed for 4 h in methanol to obtain chiral pyrazole **197** as a pale yellow solid in good yield after recyrstalization (Scheme 3.13).



213 **197**

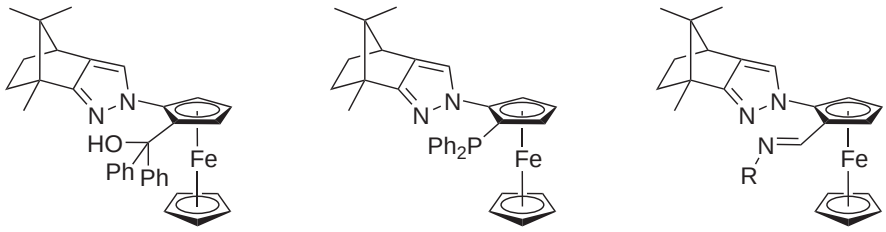
Scheme 3.13: The second step in the synthesis of chiral pyrazole **197**.

3.4.2 Pyrazole as a Directing Group on Ferrocenes

It is well-established that 1,2- and 1,1'-disubstituted ferrocenes are very useful as versatile chiral ligands in asymmetric metal catalysis. [104, 105, 171, 193, 194] Following Ugi's pioneering work in 1970, [106] they are commonly prepared starting from monosubstituted ferrocenes by *ortho*-

[6]Using NaH, instead of KH leaded mainly starting material and unknown side products.
[7]It is in equilibrium with its keto-enol tautomer **214**

lithiation[8] with directing groups such as amines and hydrazones, [196][9] sulfoxides, [198] acetals, [199] or oxazolines [107, 152, 200] and subsequent trapping of the resulting lithium reagent with an appropriate electrophile. However, no pyrazole was utilized for this purpose. Therefore, studies were then focused on the applicability of pyrazole as *ortho*-directing group on ferrocenes and the synthesis of potential ligands such as shown in Figure 3.1.



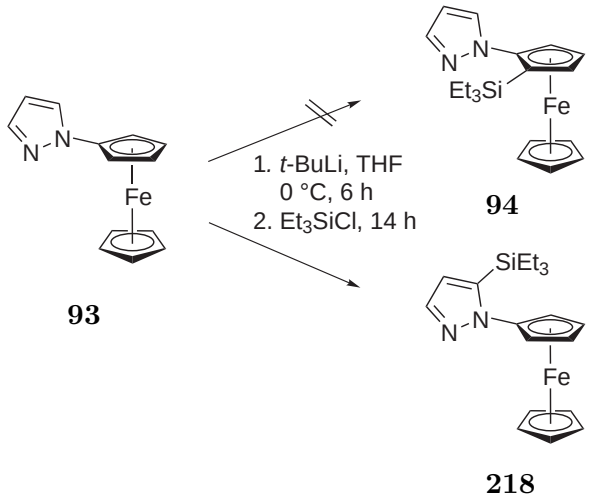
215 **216** **217**

Figure 3.1: Potential ligands having *P,O*--, *P,N*--, and *N,N*-- coordinations which could be synthesized from chiral pyrazole **197**.

Pyrazole was choosen as a model substrate for *ortho*-directing reaction and triethylchlorosilane was the electrophile of choice for quenching the lithiated species. Pyrazole **93** was treated with *sec*-BuLi in tetrahydrofuran at 0 °C and after 6 h, triethylchlorosilan was added and the mixture was stirred for 14 h at room temperature. After acidic work-up, only starting material was obtained. Changing the butyllithium species to *tert*-BuLi gave a product, whose NMR analysis showed that lithiation occured on pyrazole ring but not on ferrocene (Scheme 3.14).

[8]For a recent review illustrating the major advances in directed lithiations (by complex induced proximity effects), see: [195]

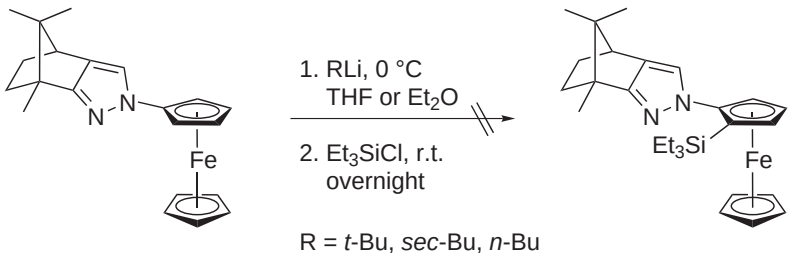
[9]For a review about the use of chiral hydrazones, see: [197]



93 **94** **218**

Scheme 3.14: Lithiation of pyrazole with *tert*-BuLi in THF at 0 °C.

This results showed that achiral pyrazole **93** was not a good model substrate since it has also some other positions which could be lithiated with *tert*-BuLi. Therefore, chiral pyrazole **95** was used for further test reaction. It was treated with *tert*-BuLi at 0 °C in tetrahydrofuran and after 3 h, triethylchlorosilan was added and the mixture was stirred at room temperature for 16 h. Unfortunately no product was obtained. Changing the solvent to the diethylether and applying the same conditions did not afford the desired product and only starting material was recovered. Using *sec*-BuLi and *n*-BuLi in diethylether had no positive effect on the reaction and only starting material was recovered after acidic work-up (Scheme 3.15).



95 **96**

Scheme 3.15: Lithiation of chiral pyrazole **197** with different BuLi species in THF or Et_2O at 0 °C.

3.4.3 Bispyrazoles as Potential Ligands

As a subsequent study, complexation of bispyrazoles **208** and **209** with Cu (II) salts was studied. Unfortunately, no complexes was obtained with the copper salts shown in Table 3.2.

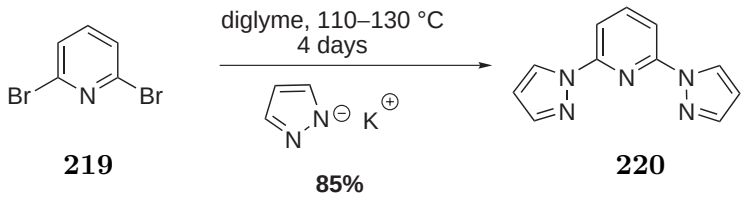
Table 3.2: Complexation study of bispyrazol **208** and **209** with various copper salts in different solvents.

Entry	Bispyrazole	Cu-salt	Solvent	Co-ligand	Product
1	**208**	$Cu(SO_4)_2$	CH_3OH	–	–
2	**208**	$CuCl_2$	CH_3OH	–	–
3	**208**	$Cu(OTf)_2$	CH_3CN	KBr	–
4	**208**	$Cu(ClO_4)_2.6H_2O$	CH_3CN	KBr	–
5	**208**	CuI	CH_3CN	–	–
6	**209**	$Cu(OTf)_2$	CH_3OH	–	–
7	**209**	$Cu(ClO_4)_2.6H_2O$	CH_3CN	KBr	–

3.4.4 A Small Extension of Bispyrazoles

After the discovery of 2,6-bis(*N*-pyrazolyl)pyridine (bpp) by Jameson and Goldsby, [201] much work has been carried out in the past decades with various transition metals and the bpp because of its potential in binding to metal atoms.[10]

Since, 2-position of pyridine is labile to the nucleophilic substitution reaction, the synthesis of bpp (**220**) could be achieved by nucleophilic substitution reaction of 2,6-dibromopyridine (**219**) with potassium salt of pyrazole under long reactiong time (4 days) and harsch conditions ($110 - 130$ °C) (Scheme 3.16). [201]



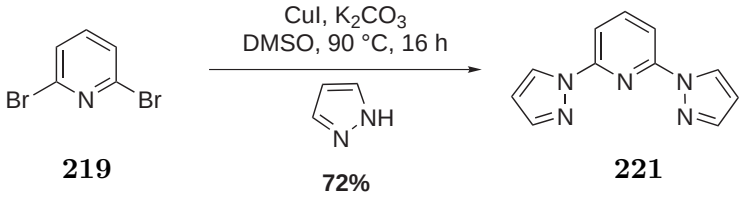
219 **85%** **220**

Scheme 3.16: The first synthesis of bpp by double substitution reaction.

[10] For a representative examples, see: [202]

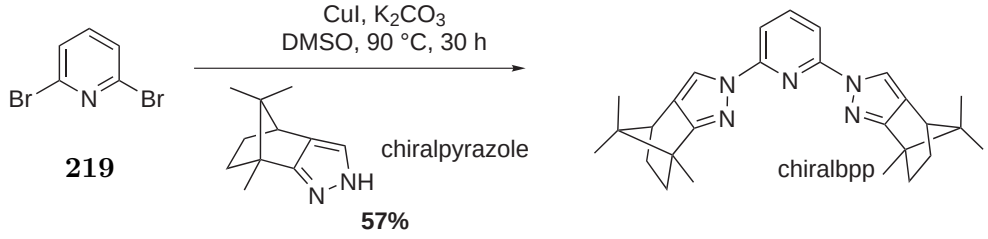
Interestingly, the metal-mediated or catalyzed coupling reaction has not been reported yet. Therefore, the project was slightly extended to the synthesis of bpp *via* copper-mediated coupling reaction.

For this purpose, dibromopyridine **219** was treated with pyrazole in the presence of CuI as a coupling mediator and K_2CO_3 as a base in DMSO at 90 °C for 16 h and bpp was obtained in 72% yield (Scheme 3.17).



Scheme 3.17: Copper-mediated synthesis of bpp under milder conditions.

Synthesis of chiral bpp **221** was previously reported by Steel [203] by using classical nuclophilic substitution reaction of dibromopyridine **219** with excess amount (four equivalents) of *in situ* prepared potassium salt of chiral pyrazole **197** in diglyme at 120 °C–130 °C in 70% yield after 3-4 days. Using coupling reaction method, chiral bpp **221** was obtained in 57% yield upon the reaction of dibromopyridine **219** with chiral pyrazole **197** in the presence of CuI and K_2CO_3 at 90 °C in DMSO after 30 h (Scheme 3.18).



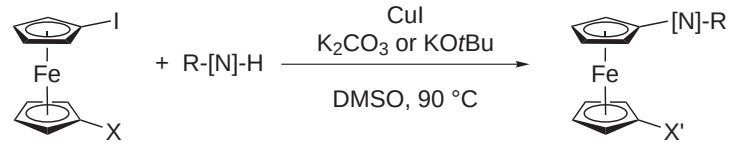
Scheme 3.18: Copper-mediated synthesis of bpp under milder conditions.

As a result, the syntheses of bpp (**220**) and chiral bpp **221** were achieved in good yields at milder temperature with shorter reaction time, using mild bases and a cheap metal-mediator.

As a subsequent study, complexation of chiral bpp **221** with Cu (II) salts was studied. Neither $Cu(ClO_4)_2$ nor $Cu(OTf)_2$ in the presence of KBr as a co-ligand in CH_3CN and subsequent evaporation afford the Cu (II) complex of chiral bpp **221**.

3.5 Summary and Outlook

In this part of the thesis, a simple and efficient method for the preparation of various *N*-substituted ferrocene by Ullmann type coupling reaction mediated by copper(I) iodide was presented. Attractive features of this protocol are the direct synthesis of such valuable compounds by C–N bond formation and the use of simple and cheap reagents (metal salt and base).



193 X = H
196 X = I

X' = H, [N]-R

Scheme 3.19: General synthesis of *N*-substituted ferrocenes

Moreover, pincer-type bispyrazolylpyridine **220** and **221** were also synthesized by means of this method in good yield at milder temperature with shorter reaction time, using mild bases and a cheap metal-mediator, compared to literature protocols. [201, 203]

Ferrocenyl imidazole **201** and triazole **202** are interesting compound which could be valuable precursors in *N*-heterocyclic carbene chemistry (Figure 3.2).

201 **202**

Figure 3.2: Structure of imidazole **201** and triazole **202**.

Unfortunately, *ortho*-lithiation of pyrazole **95** was not achieved so far, but after further investigation, a route to new-type of chiral ferrocenyl potential ligands could be opened.

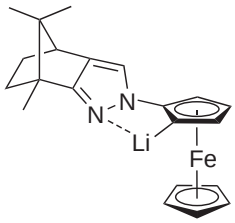
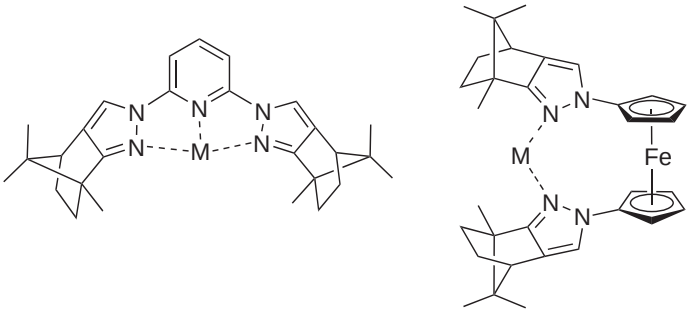


Figure 3.3: *ortho*-Lithiated chiral pyrazole **95**

Although no metal complex of 1,1'-bispyrazolyl ferrocene **208**, its chiral derivative **209** and chiral bpp **221** with Cu(I) and Cu(II) salts was obtained, By means of further investigations, they could serve as achiral and chiral ligands for various transition metals.



Chapter 4

Experimental Section

4.1 General Methods and Chemicals

All reactions involving air- or moisture-sensitive compounds were carried out under argon using standard Schlenk and vacuum line techniques. [204] Glassware were heated under vacuum with a heat gun and flushed with argon. Addition of all reagents as well as solvents was carried out with glass or polypropylene syringes equipped with V2A steel needles under argon steam. Chemicals which are labile to air were kept in a glove-box or refrigerator and stored under argon.

4.1.1 Solvents

The solvents were dried and distilled under argon according to standard procedures: [205]
Acetone: was purchased from Fluka and used as received. Acetonitrile: was purchased from Sigma-Aldrich and used as supplied. CCl_4: was purchased from Merck and used as received. CH_2Cl_2: was distilled from CaH_2 under Ar. Diethyl ether: was predried over KOH distilled from sodium benzophenone ketyl radical under argon. DMF: was purchased from Merck and used as received. DMSO: was purchased from Merck and used as received and stored over 4 Å molecular sieves. Methanol: analytically pure MeOH required for the desymmetrization was purchased from Fluka or Merck and used as supplied. THF: was predried over KOH and distilled from sodium benzophenone ketyl radical under argon. Toluene: was distilled from sodium benzophenone ketyl radical under argon and stored over 4 Å molecular sieves.
Unless otherwise specified, all reagents were purchased from commercial suppliers (Acros, Aldrich, Fisher-Scientific, Fluka, Lancaster, Merck, Strem) and used without further purification. All the amino acids employed in practice were received from Degussa.

4.1.2 Determination of the Physical Data

^{1}H NMR Spectra

^{1}H NMR spectra were recorded at room temperature on a Varian VXR 300 (300 MHz), Varian Gemini 300 (300 MHz) or Inova 400 (400 MHz) spectrometer. The chemical shifts are given in ppm using tetramethylsilane (δ = 0.00 ppm) as internal standard, and in the absence of tetramethylsilane, they are based on the deuterated solvent peak (Chloroform δ = 7.25 ppm). The coupling constants J are given in Hertz. The following abbreviations are used in order to describe the signals observed in the ^{1}H NMR-spectra: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), bs (broad signal). The diastereomeric ratio (dr) was determined by analysis of the ^{1}H NMR-spectra of the crude reaction product.

^{13}C NMR Spectra

^{13}C NMR spectra were ^{13}C-broad band-decoupled and measured with a Varian VXR 300 (75 MHz), Varian Gemini 300 (75 MHz) or Inova 400 (100 MHz) spectrometer. The chemical shifts are given in ppm using tetramethylsilane (δ = 0.00 ppm) or the deuterated solvent peak as internal standard.

Mass spectrometry

Mass spectra were recorded on a Varian MAT 212 and a Finnigan MAT 95 spectrometer. All values are given in atomic units of mass per elemental charge (m/z). The intensity is given as a percentage of the base peak.

IR-spectroscopy

Infrared spectra were recorded on a Perkin-Elmer PE-1760 FT apparatus. All bands are given in cm^{-1}. Only the strongest bands (50-100%) are listed.

Optical rotation

Optical rotations were determined on a Perkin Elmer PE-241 instrument at room temperature (ca. 20 °C) using solvents of Merck UVASOL-quality. The measurements were carried out using a light frequency of 589 nm (D-line of a sodium vapour lamp) in a cuvette (length d = 10 cm; concentration c is given in g/100 mL).

Melting point

Melting Points were measured in open glass capillaries with a Büchi B-540 apparatus and are uncorrected.

Elemental analysis

All microanalyses were conducted on a Heraeus CHN RAPID instrument. All values are given as mass percentages.

Chromatography

Thin layer chromatography (TLC):
TLC was performed using precoated aluminium backed sheets (Merck silica gel 60 F254). Detection was performed by using UV radiation (254 nm).
Column chromatography:

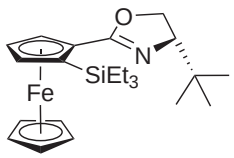
Separations by column chromatography were conducted according to the suggestion of Still. [206] Silica gel 60 (Merk, mesh 40-63 μm) was employed as stationary phase. All solvents have been distilled prior to use.

4.2 C–H Activation of Ferrocene Compounds

4.2.1 General Procedure A for C–H Activation Reactions

To a solution of substrate (0.2 mmol) in toluene (0.2 mL) was added the catalyst (0.02 mmol), triethylsilane (0.16 mL, 1 mmol) and *tert*-butyl ethylene (0.12 mL, 1 mmol) under argon atmosphere. The reaction mixture was heated up to 135 °C in a closed vessel and maintained for 20 h with stirring. After cooling, the reaction mixture was separated by column chromatography using pentane/diethyl ether mixture as eluent.

4.2.2 Synthesis of (*S*,R_p)-2-(triethylsilane)ferrocenyl-5-*tert*-butyloxazoline - (*S*,R_p)-75



It was synthesized according to general procedure A, starting from ferrocenyl-5-*tert*-butyloxazoline (0.2 mmol, 62 mg) using 10 mol% of $Ru(H)_2(CO)(PPh_3)_3$ as catalyst in 33% yield as an orange oil (28 mg, diastereomeric ratio = 90:10). Eluent: pentane/diethyl ether = 90/10.

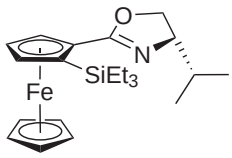
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87–0.95 (m, 24H, -Si(CH_2CH_3)$_3$, -C(CH_3)$_3$), 3.79 (dd, J = 8.2 Hz, 10.1 Hz, 1H, -CHN), 4.00 (t, J = 8.2 Hz, 1H, -CH_2O), 4.09 (s, 5H, C_5H_5), 4.11 (s, 5H, C_5H_5) (due to diastereomer) 4.14 (dd, J = 8.4 Hz, 10.1 Hz, 1H, -CH_2O), 4.17 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.38 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.82 (dd, J = 1.5 Hz, 2.5 Hz, -C_5H_3) (due to diastereomer), 4.84 (dd, J = 1.5 Hz, 2.5 Hz, -C_5H_3).
^{13}C NMR (75 MHz, $CDCl_3$): δ 4.4 (CH_2) (due to diastereomer), 4.8 (CH_2), 6.7 (CH_3) (due to diastereomer), 8.1 (CH_3), 26.1 (CH_3), 33.6 (C), 68.1 (CH_2), 69.5(CH), 71.6 (CH), 72.9 (CH), 76.3 (CH), 77.3 (CH), 165.8 (C).

MS (EI, 70 eV): m/z(%) 425 (M^+, 100), 396 (46), 368 (11), 296 (20), 268 (10).

$[\alpha]_D^{25}$ –28.1 (c 2.1, $CHCl_3$).

HRMS for $C_{23}H_{35}FeNOSi$: calcd. 425.1837, found 425.1838.

4.2.3 Synthesis of (S,R_p)-2-(triethylsilane)ferrocenyl-5-*iso*-propyloxazoline - [(S,R_p)-79]



It was synthesized according to general procedure A, starting from ferrocenyl-5-*iso*-propyl-oxazoline (0.2 mmol, 60 mg) using 10 mol% of $Ru(H)_2(CO)(PPh_3)_3$ as catalyst in 60% yield as an orange oil (49 mg, diastereomeric ratio = 62:38). Eluent: pentane/diethyl ether = 90/10.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.70–0.95 (m, 15H, -Si(CH_2CH_3)$_3$ + diastereomer), 0.91 (d, J = 6.0 Hz, 3H, -CH(CH_3)$_2$), 0.95 (d, J = 6.7 Hz, 3H, -CH(CH_3)$_2$), 1.66–1.77 (m, 1H, -CH(CH_3)$_2$), 1.67–1.78 (m, 1H, -CH(CH_3)$_2$)(due to diasetereomer), 3.82–3.95 (m, 1H, -NCH + diasteromer), 4.09 (s, 5H, C_5H_5), 4.10 (s, 5H, C_5H_5) (due to diastereomer), 4.16–4.21 (m, 1H, -CH_2O + diastereomer), 4.38 (t, J = 2.5 Hz, 1H, -C_5H_3) (due to diastereomer), 4.39 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.84 (dd, J = 1.2 Hz, 2.5 Hz, 1H, -C_5H_3) (due to diastereomer), 4.86 (dd, J = 1.5 Hz, 2.5 Hz, 1H, -C_5H_3).

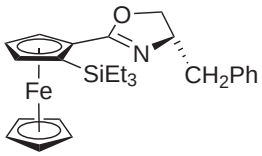
^{13}C NMR (75 MHz, $CDCl_3$): δ 4.5 (CH_2) (due to diastereomer), 4.7 (CH_2), 7.1 (CH_3) (due to diastereomer), 8.8 (CH_3), 20.2 (CH_3), 22.2 (CH_3), 32.4 (CH), 32.5 (CH) (due to diastereomer), 68.2 (CH_2), 68.3 (due to diastereomer), 69.0(CH), 69.1 (CH) (due to diastereomer), 70.2 (CH), 70.5 (C), 70.6 (CH) (due to diastereomer), 72.3 (CH), 72.5 (CH) (due to diastereomer), 165.7 (C).

MS (EI, 70 eV): m/z(%) 411 (M^+ , 95), 382 (100), 296 (30), 268 (19).

$[\alpha]_D{}^{25}$ –70.0 (c 0.7, $CHCl_3$).

HRMS for $C_{22}H_{33}FeNOSi$: calcd. 411.1681, found 411.1680.

4.2.4 Synthesis of (S,R_p)-2-(triethylsilane)ferrocenyl-5-benzyloxazoline[(S,R_p)-81]



It was synthesized according to general procedure A, starting from ferrocenyl-5-benzyloxazoline (0.2 mmol, 69 mg) using 10 mol% of $Ru(H)_2(CO)(PPh_3)_3$ as catalyst in 72% yield as an orange oil (66 mg, diastereomeric ratio = 58:42). Eluent: pentane/diethyl ether = 90/10.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69–0.95 (m, 15H, -Si(CH_2CH_3)$_3$ + diastereomer), 2.56 (dd, J = 9.3 Hz, 13.7 Hz, 1H, -CH_2Ph), 2.67 (dd, J = 8.0 Hz, 13.7 Hz, 1H, -CH_2Ph) (due to diastereomer), 3.06 (dd, J = 5.5 Hz, 13.7 Hz, 1H, -CH_2Ph) (due to diastereomer), 3.16 (dd, J = 4.7 Hz, 13.7 Hz, 1H, -CH_2Ph), 3.91–3.97 (m, 1H, -NCH + diasteromer), 4.08 (s, 5H, C_5H_5) (due to diastereomer), 4.11 (s, 5H, C_5H_5), 4.12–4.21 (m, 2H, -CH_2O + diastereomer), 4.29–4.39 (m, 1H, -C_5H_3 + diastereomer), 4.42 (dt, J = 2.5 Hz, 5.0 Hz, 1H, -C_5H_3 + diastereomer), 4.90 (dt, J = 1.4 Hz, 2.5 Hz, 1H, -C_5H_3 + diastereomer), 7.13–7.28 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ 5.0 (CH_2), 8.2 (CH_3), 41.9 (CH_2), 67.7 (C), 67.8 (C) (due to diastereomer), 69.8 (CH), 71.4 (CH_2), 72.1 (CH), 73.2 (CH), 73.2 (CH) (due to diastereomer), 77.6 (CH), 77.7 (CH) (due to diastereomer), 126.4 (CH), 128.5 (CH), 128.5 (CH) (due to diastereomer), 129.2 (CH), 129.4 (CH)(diastereomer), 138.2(C).

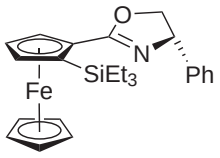
IR (KBr): ν 2951, 1652, 1455, 1237, 1138 cm^{-1}.

MS (EI, 70 eV): m/z(%) 459 (M^+, 93), 430 (100), 296 (18), 268 (14).

$[\alpha]_D{}^{25}$ +22.2 (c 1.0, $CDCl_3$).

HRMS for $C_{22}H_{33}FeNOSi$: calcd. 459.1681, found 459.1681.

4.2.5 Synthesis of (S,R_p)-2-(triethylsilane)ferrocenyl-5-phenyloxazoline[(S,R_p)-80]



It was synthesized according to general procedure A, starting from ferrocenyl-5-phenyloxazoline (0.2 mmol, 66 mg) using 10 mol% of $Ru(H)_2(CO)(PPh_3)_3$ as catalyst in 65% yield as an orange oil (58 mg, diastereomeric ratio = 60:40). Eluent: pentane/diethyl ether = 90/10.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69–0.95 (m, 15H, -Si(CH_2CH_3)$_3$ + diastereomer), 4.08 (t, J = 8.0 Hz, 1H, -NCH), 4.08 (t, J = 8.0 Hz, 1H, -NCH) (due to diastereomer), 4.14 (s, 5H, C_5H_5) (due to diastereomer), 4.15 (s, 5H, C_5H_5), 4.21–4.24 (m, 1H, -CH_2O + diastereomer), 4.43 (t, J = 3.5 Hz, 1H, -C_5H_3), 4.45 (t, J = 3.5 Hz, 1H, -C_5H_3) (due to diastereomer), 4.58 (dt, J = 8.2 Hz, 9.9 Hz, 1H, -CH_2O), 4.95 (dd, J = 1.4 Hz, 2.5 Hz, 1H -C_5H_3), 5.00 (dd, J = 1.4 Hz, 2.5 Hz, 1H -C_5H_3), 5.14 (ddd, J = 3.3 Hz, 8.0 Hz, 9.9 Hz, 1H, -CH_2O + diastereomer).

^{13}C NMR (100 MHz, $CDCl_3$): δ 5.1 (CH_2), 5.1 (CH_2) (due to diastereomer), 8.2 (CH_3), 8.3 (CH_3) (due to diastereomer), 69.8 (CH), 69.8 (CH) (due to diastereomer) 71.5 (C), 72.1 (CH), 72.2 (CH) (due to diastereomer), 73.3 (CH), 73.4 (CH) (due to diastereomer), 74.2 (CH_2), 74.4 (CH_2) (due to diastereomer), 77.7 (CH), 77.8 (CH) (due to diastereomer), 126.6 (CH) (due to diastereomer), 126.8 (CH), 127.4 (CH), 128.6 (CH), 128.7 (CH) (due to diastereomer), 142.6(C), 143.0 (C), 167.8 (C).

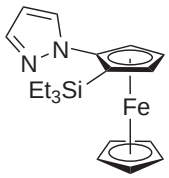
IR (KBr): ν 2952, 1649, 1456, 1236, 1136 cm^{-1} .

MS (EI, 70 eV): m/z(%) 445 (M^+, 63), 416 (100), 299 (12), 268 (10).

$[\alpha]_D^{25}$ +92.6 (c 0.5, $CHCl_3$)

HRMS for $C_{21}H_{31}FeNOSi$: calcd. 445.1524, found 459.1525.

4.2.6 Synthesis of 2-(triethylsilane)-1-pyrazolyl-ferrocene (94)



It was synthesized according to general procedure A starting from *N*-ferrocenyl pyrazole (**93**) (0.2 mmol, 50 mg), using 10 mol% of $Ru(H)_2(CO)(PPh_3)_3$ as catalyst in 35% yield as an orange oil (26 mg). Eluent: pentane/diethyl ether = 95/5.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63–0.78 (m, 6H, -Si(CH_2CH_3)$_3$), 0.94 (t, J = 8.0 Hz, 9H, -Si(CH_2CH_3)$_3$), 4.10 (dd, J = 1.4 Hz, 2.2 Hz, 1H, -C_5H_3), 4.27 (s, 5H, -C_5H_5), 4.32 (t, J = 2.2 Hz, 1H, -C_5H_3), 4.59 (dd, J = 1.4 Hz, 2.2 Hz, 1H, -C_5H_3), 6.29 (t, J = 2.2 Hz, 1H, -CH), 7.52 (d, J = 1.6 Hz, 1H, -NCH), 7.73 (d, J = 2.20 Hz, 1H, -CHN).

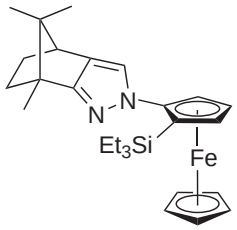
^{13}C NMR (100 MHz, $CDCl_3$): δ 4.7 (CH_2), 8.0 (CH_3), 67.4 (CH), 67.5 (CH), 69.9 (CH), 72.7 (CH), 105.7 (CH), 131.5 (CH), 139.5 (CH).

IR (KBr): ν 2952, 1520, 1410, 1110 cm^{-1}.

MS (EI, 70 eV): m/z(%) 366 (M^+, 40), 337 (100).

Anal. Calcd. for $C_{19}H_{26}FeN_2OSi$: C, 62.29; H, 7.15; N, 7.65. Found: C, 62.11; H, 7.34; N, 7.61.

4.2.7 Synthesis of 1-[(4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl]-2-triethylsilyl ferrocene [(4*S*,7*R*,R_p)-96]



It was synthesized according to general procedure A, starting from 1-[(4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl]-ferrocene (**197**) (0.2 mmol, 72 mg) using 10 mol% of $Ru(H)_2(CO)(PPh_3)_3$ as catalyst in 21% yield as an orange oil (20 mg, diastereomeric ratio = 73:27). Eluent: pentane/diethyl ether = 95/5.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67–0.78 (m, 6H, -Si(CH_2CH_3)$_3$ + diasteromer), 0.71 (s, 3H, -C(CH_3)$_2$ + diastereomer), 0.92–0.98 (m, 9H, -Si(CH_2CH_3)$_3$ + diastereomer), 0.94 (s, 3H, -C(CH_3)$_2$ + diastereomer), 1.14–1.21 (m, 1H, -CH_2 + diastereomer), 1.26 (s, 3H, -CH_3 + diastereomer), 1.27–1.37 (m, 1H, -CH_2 + diastereomer), 1.78–1.87 (m, 1H, -CH_2 + diastereomer), 2.03–2.13 (m, 1H, -CH_2 + diastereomer), 2.77 (d, J = 3.8 Hz, 1H, -CH + diastereomer), 4.02–4.04 (m, 1H, -C_5H_3 + diastereomer), 4.20 (s, 5H, -C_5H_5) (due to diastereomer), 4.21 (s, 5H, -C_5H_5), 4.25–4.27 (m, 1H, -C_5H_3 + diastereomer), 4.48–4.49 (m, 1H, -C_5H_3) (due to diastereomer), 4.49 (dd, J = 1.4 Hz, 2.5 Hz, 1H, -C_5H_3), 7.32 (s, 1H, -CH), 7.32 (s, 1H, -CH) (due to diastereomer).

^{13}C NMR (100 MHz, $CDCl_3$): δ 4.7 (CH_2), 4.8 (CH_2) (due to diastereomer), 8.1 (CH_3), 8.2 (CH_3) (due to diastereomer), 10.9 (CH_3), 19.3 (CH_3), 20.5 (CH_3) (due to diastereomer), 20.8 (CH_3), 28.0 (CH_2) (due to diastereomer), 28.3 (CH_2), 33.8 (CH_2) (due to diastereomer), 33.9 (CH_2), 47.4 (CH) (due to diastereomer), 47.5 (CH), 50.2 (C), 66.1 (C), 66.5 (CH), 67.8 (CH), 69.7 (CH), 72.3 (CH), 122.7 (CH) (due to diastereomer), 123.1 (CH).

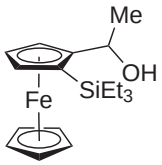
IR (KBr): ν 2952, 1946, 1506, 1405, 1004 cm^{-1}.

MS (EI, 70 eV): m/z(%) 474 (M^+, 85), 445 (100).

$[\alpha]_D^{25}$ +2.5 (c 1.6, $CDCl_3$).

Anal. Calcd. for $C_{27}H_{38}FeN_2Si$: C, 68.34; H, 8.07; N, 5.90. Found: C, 68.56; H, 7.99; N, 6.12.

4.2.8 Synthesis of 1-(α-triethylsilane)ferrocenyl-1-ethanol (91)



It was synthesized according to general procedure A, starting from (1-ethanol)-ferrocene (0.2 mmol, 46 mg) using 10 mol% of $Ru(H)_2(CO)(PPh_3)_3$ as catalyst in 65% yield as an orange oil (45 mg). Eluent: pentane/diethyl ether = 95/5.

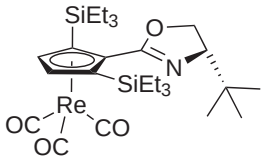
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.54 (q, J = 8.0 Hz, 9H, -Si(CH_2CH_3)$_3$), 0.90 (t, J = 8.0 Hz, 6H, -Si(CH_2CH_3)$_3$), 1.42 (d, J = 6.3 Hz, 3H, -CH_3), 3.99–4.02 (m, 1H, -C_5H_3), 4.03–4.05 (m, 1H, -C_5H_3), 4.06 (s, 5H, -C_5H_5), , 4.12–4.14 (m, 1H, -C_5H_3), 4.63 (q, J = 6.3 Hz, 1H, -CHOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 5.3 (CH_2), 7.2 (CH_3), 24.2 (CH_3), 65.8 (CH), 66.4 (CH), 67.4 (CH), 67.5 (C), 67.7 (CH), 68.6 (CH).

MS (EI, 70 eV): m/z(%) 344 (M^+, 100), 326 (31), 223 (29), 213 (18).

Anal. Calcd. for $C_{18}H_{28}FeOSi$: C, 62.78; H, 8.20. Found: C, 62.60; H, 8.16.

4.2.9 Synthesis of (S,R_p)-2-(triethylsilane)cyrhetrenyl-5-*tert*-butyloxazoline [(S,R_p)-100]



It was synthesized according to general procedure A, starting from cyrhetrenyl-5-*tert*-oxazoline (0.2 mmol, 93 mg) using 10 mol% of $Ru(H)_2(CO)(PPh_3)_3$ as catalyst in 72% yield as an orange oil (100 mg). Eluent: pentane/diethyl ether = 95/5.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.69–0.95 (m, 15H, -Si(CH_2CH_3)$_3$), 3.82 (m, 2H, -NCH + -CH_2O), 4.21 (dd, J = 7.4 Hz, 9.1 Hz, 1H, -CH_2O), 5.26 (d, J = 2.7 Hz, 1H, -CH), 5.36 (d, J = 2.7 Hz, 1H, -CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 4.9 (CH_2), 5.1 (CH_2), 7.8 (CH_3), 7.9 (CH_3), 26.1 (CH_3), 33.5 (C), 68.5 (CH_2), 76.9 (CH), 92.7 (C), 94.6 (CH), 96.0 (CH), 194.4 (C).

IR (KBr): ν 3436, 2020, 1918 cm^{-1} .

MS (EI, 70 eV): m/z(%) 689 (M^+-3, 8), 660 (100), 560 (15), 83 (13).

Anal. Calcd. for $C_{27}H_{47}NO_4ReSi_2$: C, 46.86; H, 6.85; N, 2.02. Found: C, 46.77; H, 6.91; N, 1.77.

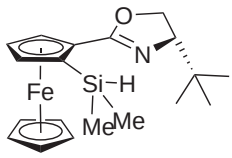
4.3 Synthesis of Organosilanols

4.3.1 Synthesis of silanes 152: General Procedure B

Ferrocenyl silanes **152** have been synthesized according to the following general procedure, which had previously been applied in slightly different form for the synthesis of diastereomerically pure ortho-substituted ferrocenyl oxazolines. [151]

A solution of ferrocenyl oxazoline **77** (1 mmol) in dry THF (20 mL) was prepared at room temperature under argon atmosphere and cooled to −78 °C (by using a dry ice/acetone mixture). After being treated dropwise with *sec*-BuLi (1.0 mL, 1.3 mmol, 1.3 M in cyclohexane), the mixture was stirred for 2 hours at the same temperature. The addition of sec-BuLi changed the color of the solution from orange to red. The respective chlorosilane (1.5 mmol) was added dropwise, and the solution was allowed to warm to room temperature overnight. After washing with water (20 mL) and phase separation, the aqueous phase was extracted with CH_2Cl_2 (10 mL) until the aqueous phase became colorless. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography with a suitable solvent system (pentane/diethyl ether) was used for the purification of the resulting ferrocenyl silanes **152**. The products proved to be rather unstable, and commonly samples with purities of ca. 90% were obtained.

4.3.2 Synthesis of (*S,R*$_p$)-2-(α-dimethylsilane)ferrocenyl-5-*tert*-butyl-oxazoline [(*S,R*$_p$)-152a]



It was synthesized according to general procedure B, starting from ferrocenyl-5-*tert*-butyl-oxazoline and dimethyl-chlorosilane, in 64% yield as an orange oil. Eluent: pentane/diethyl ether = 85/15.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.29 (d, J = 3.5 Hz, 3H, -SiH(CH_3)$_2$), 0.31 (d, J = 3.7 Hz, 3H, -SiH(CH_3)), 0.89 (s, 9H, -C(CH_3)), 3.81 (dd, J = 7.4 Hz, 8.7 Hz, 1H, -CHN), 4.04–4.10 (m, 1H, -CH_2O), 4.08 (s, 5H, C_5H_5), 4.15 (dd, J = 8.7 Hz, 9.3 Hz, 1H, -CH_2O), 4.21 (dd, J = 1.2 Hz, 1.9 Hz, 1H, -C_5H_3), 4.36 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.57 (dq, J = 3.5 Hz, 3.7 Hz, 1H, -SiH(CH_3)$_2$), 4.76–4.80 (m, 1H, -C_5H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ -3.2 (CH_3), -1.7 (CH_3), 36.0 (CH_3), 33.7 (C), 68.3 (CH_3), 69.5(C), 69.9 (CH), 72.0 (CH), 73.0 (CH), 76.4 (CH).

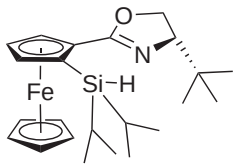
IR (KBr): ν 2957, 2140, 1657 cm^{-1} .

MS (EI, 70 eV): m/z(%) 369 (M$^+$, 100), 354 (28), 312 (30), 195 (21), 121 (12).

$[\alpha]_D^{25}$ –126.7 (*c* 3.0, $CDCl_3$).

HRMS for $C_{19}H_{19}FeNOSi$: calcd. 369.1211, found 369.1212.

4.3.3 Synthesis of (S,R_p)-2-(α-diisopropylsilane)ferrocenyl-5-*tert*-butyloxazoline [(S,R_p)-152b]



It was synthesized according to general procedure B, starting from ferrocenyl-5-*tert*-butyloxazoline and diisopropylchlorosilane, in 64% yield as an orange oil. Eluent: pentane/diethyl ether = 85/15.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 9H, -C(CH_3)$_3$), 0.97 (d, J = 7.7 Hz, 3H, -CH(CH_3)$_2$), 1.01 (d, J = 7.7 Hz, 1H, -CH(CH_3)$_2$), 1.20 (d, J =6.9 Hz, 3H, -CH(CH_3)$_2$), 1.25 (d, J = 6.6 Hz, 3H, -CH(CH 3)$_2$), 1.30-1.40 (m, 2H, -CH(CH_3)$_2$), 3.88 (dd, 1H, J = 8.0 Hz, 10.0 Hz, -CHN), 4.09 (t, J = 8.2 Hz, 1H, -CH_2O), 4.15 (s, 5H, C_5H_5), 4.23 (dd, J = 8.5 Hz, 10.1 Hz, 1H, -CH_2O), 4.29 (dd, J = 1.4 Hz, 2.4 Hz, 1H, -C_5H_3), 4.31 (t, J = 1.6 Hz, 1H, -SiH(CH(CH_3)$_2$)$_2$), 4.47 (t, J = 2.20 Hz, 1H, -C_5H_3), 4.92 (dd, J = 1.4 Hz, 2.4 Hz, 1H, -C_5H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8 (CH), 12.3 (CH), 18.8 (CH_3), 19.3 (CH_3), 19.6 (CH_3), 20.7 (CH_3), 26.0 (CH_3), 33.5 (C), 68.0 (CH_2), 68.1 (C), 69.7 (C), 70.0 (CH), 72.0 (CH), 72.3 (CH), 76.2 (CH), 77.3 (CH), 165.4 (C).

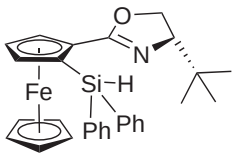
IR (KBr): ν 2951, 2125, 1657 cm^{-1}.

MS (EI, 70 eV): m/z(%) 425 (M^+, 41), 382 (100), 282 (22).

$[\alpha]_D^{25}$ +36.0 (c 0.5, $CHCl_3$).

HRMS for $C_{23}H_{35}FeNOSi$: calcd. 425.1837, found 425.1837.

4.3.4 Synthesis of (S,R_p)-2-(α-diphenylsilane)ferrocenyl-5-*tert*-butyloxazoline [(S,R_p)-152c]



It was synthesized according to general procedure B, starting from ferrocenyl-5-*tert*-butyl-oxazoline and diphenylchlorosilane, in 91% yield as a dark orange solid. Eluent: pentane/diethyl ether = 85/15.

mp. 118 – 120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (s, 9H, -C(CH_3)$_3$), 3.72 (dd, J = 8.2 Hz, 9.7 Hz, 1H, -CHN), 4.09 (t, J = 8.2 Hz, 1H, -CH_2O), 4.02–4.05 (m, 1H, -CH_2O), 4.10–4.15 (m, 1H, -C_5H_3), 4.14 (s, 5H, C_5H_5), 4.44 (t, J = 2.20 Hz, 1H, -C_5H_3), 5.00 (bs, 1H, -C_5H_3). 5.74 (s,1H, -SiHPh_2), 7.21–7.72 (m, 10H, -SiHPh_2).

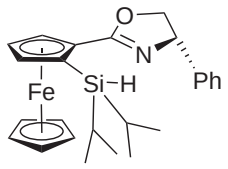
^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7 (CH_3), 33.4 (C), 66.2 (C), 68.3 (CH_2), 70.2 (CH), 72.7 (CH), 72.8 (CH), 75.8 (C), 76.1 (CH), 78.8 (CH), 127.4 (CH), 127.8 (CH), 128.8 (CH), 129.3 (CH), 135.0 (CH), 135.7 (CH), 135.8 (C), 136.0 (C), 165.3 (C).

IR (KBr): ν 2955, 2152, 1659, 1145, 1113 cm^{-1}.

MS (EI, 70 eV): m/z(%) 493 (M^+, 100), 416 (39), 409 (32).
$[\alpha]_D{}^{25}$ –52.6 (c 1.09, $CHCl_3$).

HRMS for $C_{29}H_{21}FeNOSi$: calcd. 493.1524, found 493.1525.

4.3.5 Synthesis of (*S,R*$_p$)-2-(α-diisopropylsilane)ferrocenyl-5-phenyloxazoline [(*S,R*$_p$)-152d]



It was synthesized according to general procedure B, starting from ferrocenyl-5-phenyloxazoline and diisopropylchlorosilane, in 70% yield as dark orange oil. Eluent: pentane/diethyl ether = 80/20.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (d, J = 7.2 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 0.99 (d, J = 7.4 Hz, 3H, -Si(CH(CH 3)$_2$)$_2$), 1.20 (d, J = 6.7 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 1.24 (d, J = 5.9 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 1.26-1.40 (m, 2H, -Si(CH(CH_3)$_2$)$_2$), 4.09 (t, J = 8.4 Hz, 1H, -CH_2O), 4.20 (s, 5H, C_5H_5), 4.21 (s, 5H, C_5H_5) (due to diastereomer), 4.30 (t, J = 2.1 Hz, 1H, -SiH(CH(CH_3)$_2$)$_2$), 4.34 (dd, J = 1.5 Hz, 2.5 Hz, 1H, -C_5H_3), 4.53 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.62 (dd, J = 8.2 Hz, 9.9 Hz, 1H, -CH_2O) (due to diastereomer), 4.72 (dd, J = 8.2 Hz, 9.9 Hz, 1H, -CH_2O), 5.05 (dd, J = 1.2 Hz, 2.5 Hz, -C_5H_3), 5.11 (dd, J = 1.2 Hz, 2.5 Hz, 1H, -C_5H_3), 5.18-5.28 (m, 1H, -CHN-), 7.23–7.40 (m, 5H, -Ph).
^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7 (CH), 12.36 (CH), 12.43 (CH) (due to diastereomer), 18.9 (CH_3) (due to the diastereomer), 19.0 (CH_3), 19.4 (CH_3), 19.5 (CH_3), 20.5 (CH_3), 68.3 (CH), 68.4 (CH) (due to the diastereomer), 69.7 (CH), 70.0 (CH) (due to the diastereomer), 70.2 (CH), 72.6 (CH), 72.7 (CH) (due to the diastereomer), 74.4 (CH_2), 77.8 (CH), 126.6 (CH) (due to the diastereomer), 126.7 (CH), 127.39 (CH), 127.44 (CH) (due to the diastereomer), 128.65 (CH), 128.69 (CH) (due to the diastereomer), 142.8 (C), 168.0 (C).

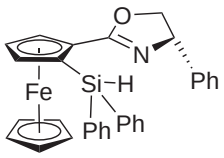
IR (KBr): ν 2942, 2124, 1649, 1458, 1139 cm^{-1}.

MS (EI, 70 eV): m/z(%) 445 (M^+, 34), 402 (100), 285 (20).

$[\alpha]_D{}^{25}$ +34.4 (c 0.61, $CHCl_3$).

HRMS for $C_{25}H_{31}FeNOSi$: calcd. 445.1524, found 445.1524.

4.3.6 Synthesis of (S,R_p)-2-(α-diphenylsilane)ferrocenyl-5-phenyloxazoline - [(S,R_p)-152e]



It was synthesized according to general procedure B, starting from ferrocenyl-5-phenyloxazoline and diphenylchlorosilane; 68% yield as dark orange solid. Eluent: pentane/diethyl ether = 85/15.

mp. 141 – 142 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65-3.72 (m, 1H, -CH_2O), 4.10 (m, 1H, -C_5H_3), 4.21 (s, 5H, C_5H_5), 4.50 (bs, 1H, -C_5H_3), 4.54–4.62 (m, 1H, -CH_2O), 5.09 (bs, 2H, -C_5H_3, -CHN), 5.76 (s, 1H, -$SiHPh_2$), 7.00–7.71 (m, 15H, -Ph, -$SiHPh_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 66.7 (C), 70.2 (CH), 70.5 (CH), 73.0 (CH), 73.2 (CH), 74.4 (CH_2), 75.1 (C), 79.2 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 127.9 (CH) 129.1 (CH), 129.5 (CH), 135.1 (CH), 135.3 (C), 135.5 (C), 135.6 (CH), 142.3 (C), 167.3 (C).

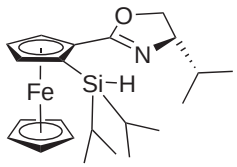
IR (KBr): ν 3064, 2146, 1642, 1151 cm^{-1}.

MS (EI, 70 eV): m/z(%) 513 (M^+, 100), 436 (39), 409 (28).

$[\alpha]_D^{25}$ +77.0 (c 0.5, $CHCl_3$).

HRMS for $C_{31}H_{27}FeNOSi$: calcd. 513.1211, found 513.1211.

4.3.7 Synthesis of (S,R_p)-2-(α-diisopropylsilane)ferrocenyl-5-*iso*-propyloxazoline [(S,R_p)-152f]



It was synthesized according to general procedure B, starting from ferrocenyl-5-*iso*-propyloxazoline and diisopropylchlorosilane, in 81% yield as dark orange oil. Eluent: pentane/diethyl ether = 80/20.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90–1.04 (m, 13H, -CH(CH_3)$_2$, -Si(CH(CH_3)$_2$)$_2$, -Si(CH-(CH_3)$_2$)$_2$), 1.19 (d, J = 6.4 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 1.22–1.38 (m, 4H, -Si(CH(CH_3)$_2$)$_2$, -Si(CH(CH_3)$_2$)$_2$), 1.73–1.86 (m, 1H, -CH(CH_3)$_2$), 3.93 (dd, J = 5.9 Hz, 7.9 Hz, 1H, -CHN-), 3.96 (m, 1H, -CH_2O), 4.16 (s, 5H, -C_5H_5), 4.26 (t, J = 2.0 Hz, 1H, -SiH(CH(CH_3)$_2$)$_2$), 4.32–4.35 (m, 1H, -CH_2O), 4.49 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.96 (dd, J = 1.2 Hz, 2.2 Hz, 1H, -C_5H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8 (CH), 12.3 (CH), 18.2 (CH_3), 18.9 (CH_3), 19.0 (CH_3), 19.4 (CH_3), 19.5 (CH_3), 20.5 (CH_3), 32.7 (CH), 68.1 (C), 69.5 (CH_2), 70.1 (CH), 72.3 (CH), 72.4 (CH), 72.5 (CH), 72.9 (C), 77.5 (CH).

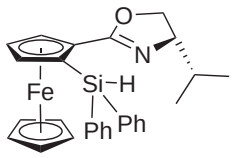
IR (KBr): ν 3098, 2953, 2126, 1657, 1140 cm^{-1}.

MS (EI, 70 eV): m/z(%) 411 (M^+, 28), 368 (100), 282 (14).

$[\alpha]_D^{25}$ +78.8 (c 0.5, $CHCl_3$).

HRMS for $C_{22}H_{33}FeNOSi$: calcd. 411.1681, found 411.1681.

4.3.8 Synthesis of (S,R_p)-2-(α-diphenylsilane)ferrocenyl-5-*iso*-propyloxazoline [(S,R_p)-152g]



It was synthesized according to general procedure B, starting from ferrocenyl-5-*iso*-propyloxazoline and diphenylchlorosilane, in 85% yield as dark orange solid. Eluent: pentane/diethyl ether = 85/15.

mp. 89 – 91 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (d, J = 6.9 Hz, 3H, -CH(CH_3)$_2$), 0.89 (d, J = 6.9 Hz, 3H, -CH(CH_3)$_2$), 1.59–1.72 (m, 1H, -CH(CH_3)$_2$), 3.57 (t, J = 8.3 Hz, 1H, -CH_2O), 3.82 (dt, J = 6.0 Hz, 8.8 Hz, 1H, -CHN), 4.03–4.06 (m, 1H, -C_5H_3), 4.15 (s, 5H, C_5H_5), 4.16–4.22 (m, 1H, -CH_2O), 4.45 (t, J = 2.2 Hz, 1H, -C_5H_3), 5.02 (bs, 1H, -C_5H_3), 5.71 (s, 1H, -SiHPh$_2$), 7.25-7.70 (m, 10H, -SiHPh$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1 (CH_3), 19.0 (CH_3), 32.5 (CH), 66.2 (C), 69.6 (CH_2), 70.3 (CH), 72.5 (CH), 72.7 (CH), 72.9 (CH), 75.8 (C), 78.9 (CH), 127.5 (CH), 127.8 (CH), 128.9 (CH), 129.3 (CH), 135.0 (CH), 135.6 (CH), 135.70 (C), 135.74 (C), 165.5 (C).

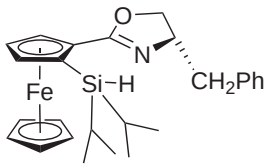
IR (KBr): ν 2958, 2139, 1658, 1117 cm^{-1}.

MS (EI, 70 eV): m/z(%) 479 (M^+, 100), 408 (54), 402 (83).

$[\alpha]_D^{25}$ +35.6 (c 0.5, $CHCl_3$).

HRMS for $C_{28}H_{29}FeNOSi$: calcd. 479.1368, found 479.1268.

4.3.9 Synthesis of (S,R_p)-2-(α-diisopropylsilane)ferrocenyl-5-benzyloxazoline [(S,R_p)-152h]



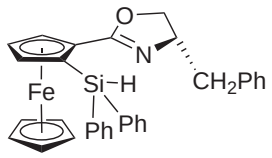
It was synthesized according to general procedure B, starting from ferrocenyl-5-benzyloxazoline and diisopropylchlorosilane, in 82% yield as dark orange oil. Eluent: pentane/diethyl ether = 80/20.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, J = 7.4 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 0.96 (d, J = 7.4 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 1.17 (d, J = 6.6 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 1.21 (d, J = 6.6 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 1.23–1.32 (m, 1H, -Si(CH(CH_3)$_2$)$_2$), 2.66–2.73 (m, 1H, -CH_2Ph), 3.15–3.21 (m, 1H, -CH_2Ph), 3.94–3.99 (m, 1H, -CH_2O), 4.11 (s, 5H, C_5H_5) (due to the diastereomer), 4.14 (s, 5H, C_5H_5), 4.15–4.30 (m, 3H, -SiH(CH(CH_3)$_2$)$_2$, -C_5H_3, -CH_2O), 4.37–4.46 (m, 1H, -CHN, 4.48–4.50 (m, 1H, -C_5H_3), 4.99 (dd, J = 1.4 Hz, 2.4 Hz, 1H, -C_5H_3), 7.17–7.34 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8 (CH) (due to diastereomer), 11.9 (CH), 12.5 (CH), 19.1 (CH_3) (due to diastereomer), 19.2 (CH_3), 19.6 (CH_3), 19.7 (CH_3), 20.6 (CH_3), 41.9 (CH_2) (due to diastereomer), 42.0 (CH_2), 67.7 (CH) (due to diastereomer), 67.8 (CH), 68.3 (C), 70.3 (CH), 71.2(CH_2), 71.4 (CH_2), 72.5 (CH), 72.6 (CH), 74.7 (C), 77.8 (CH), 126.4 (CH), 128.5 (CH), 129.4 (CH), 129.5 (CH) (due to diastereomer), 138.1 (C), 167.1 (C).

The compound was found to be rather unstable and no analytically pure samples were obtained. The product was directly converted into its oxidized counterpart (silanol **153h**).

4.3.10 Synthesis of (S,R_p)-2-(α-diphenylsilane)ferrocenyl-5-benzyloxazoline - [(S,R_p)-152i]



It was synthesized according to general procedure B, starting from ferrocenyl-5-benzyloxazoline and diphenylchlorosilane, in 60% yield as dark orange oil. Eluent: pentane/diethyl ether = 85/15.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (dd, J = 8.9 Hz, 13.6 Hz, 1H, -CH_2Ph), 2.52 (dd, J = 8.6 Hz, 13.8 Hz, 1H, -CH_2Ph) (due to diastereomer), 2.94 (dd, J = 4.7 Hz, 13.5 Hz, 1H, -CH_2Ph) (due to diastereomer), 3.08 (dd, J = 4.8 Hz, 13.7 Hz, 1H, -CH_2Ph), 3.95 (dd, J = 6.2 Hz, 8.2 Hz, 1H, -CH_2O-), 4.03–4.11 (m, 2H, -C_5H_3, -CH_2O-), 4.12 (s, 5H, C_5H_5) (due to diastereomer), 4.14 (s, 5H, C_5H_5), 4.17-4.35 (m, 1H, -CHN), 4.48 (t, J = 2.5Hz, 1H, -C_5H_3), 5.02-5.08 (m, 1H, -C_5H_3), 5.69 (s, 1H, -$SiHPh_2$), 7.08–7.77 (m, 8H, -CH_2Ph, -$SiPh_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 41.3 (CH_2) (due to diastereomer), 41.8 (CH_2), 67.4 (CH) (due to diastereomer), 67.8 (CH), 70.4 (CH), 70.5 (CH) (due to diastereomer), 71.1 (CH_2) (due to diastereomer), 71.5 (CH_2), 72.7 (CH), 73.0 (CH) (due to diastereomer), 73.2 (CH), 75.3 (C), 79.1 (CH), 79.2 (CH) (due to diastereomer), 126.5 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 129.1 (CH), 129.3 (CH), 129.5 (CH), 135.2 (CH), 135.5 (C), 135.7 (CH), 138.1 (C), 138.2 (C), 166.9 (C).

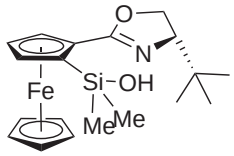
The compound was found to be rather unstable and no analytically pure samples were obtained. The product was directly converted into its oxidized counterpart (silanol **153i**).

4.4 Synthesis of ferrocenyl silanols 153

Organosilanols **153** were synthesized according to the following general procedure C, which is a slightly modified version of the published protocol [130] for the conversion of silanes to silanols.

To a solution of silane **152** (1 mmol) in acetonitrile (3 mL) was added $[IrCl(C_8H_{12})]_2$ (7 mg, 0.01 mmol) and water (36 mg, 2.0 mmol). The reaction mixture was stirred in air at room temperature or at 60 °C, and the conversion was monitored by TLC. Column chromatography or preparative TLC plates using pentane/diethyl ether mixture as eluent were utilized for the purification of the diastereomerically and enantiomerically pure organosilanols.

4.4.1 Synthesis of (S,R_p)-2-(α-dimethylsilanol)ferrocenyl-5-*tert*-butyloxazoline [(S,R_p)-153a]



It was synthesized according to general procedure C, starting from (S,R_p)-**152a**, in 91% yield as an orange solid. Eluent: pentane/diethyl ether = 90/10.

mp. 104 – 105 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.21 (s, 3H, -Si(CH_3)$_2$), 0.49 (s, 3H, -Si(CH_3)$_2$), 1.01 (s, 9H, -C(CH_3)$_3$), 3.93 (dd, 1H, J = 9.4 Hz, 9.9 Hz, -CHN), 4.14 (t, J = 8.8 Hz, 1H, -CH_2O), 4.23 (s, 5H, -C_5H_5), 4.26 (dd, J = 1.4 Hz, 2.4 Hz, 1H, -C_5H_3), 4.29 (dd, J = 8.8 Hz, 9.9 Hz, 1H, -CH_2O), 4.48 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.82 (dd, J = 1.4 Hz, 2.5 Hz, 1H, -C_5H_3), 7.83 (bs, 1H, -OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0 (CH_3), 2.91 (CH_3), 25.98 (CH_3), 33.0 (C), 68.4 (CH_2), 69.8 (CH), 72.1 (CH), 72.5 (CH), 72.8 (C), 73.9 (C), 75.2 (CH), 76.3 (CH), 168.7 (C).

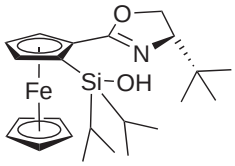
IR (KBr): ν 3441, 2858, 1643, 1149 cm^{-1}.

MS (EI, 70 eV): m/z(%) 385 (M^+, 100), 328 (27).

$[\alpha]_D{}^{25}$ –309.6 (*c* 0.5, $CHCl_3$).

Anal. Calcd. for $C_{19}H_{27}FeNO_2Si$: C, 59.22; H, 7.06; N, 3.63; found C, 58.90; H, 7.41; N, 3.55.

4.4.2 Synthesis of (*S,R*$_p$)-2-(α-diisopropylsilanol)ferrocenyl-5-*tert*-butyloxazoline [(*S,R*$_p$)-153b]



It was synthesized according to general procedure C, starting from (*S,R*$_p$)-**152b**, in 77% yield as a dark orange oil. Eluent: pentane/diethyl ether = 90/10.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (d, J = 7.14 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 0.88 (d, J = 7.14 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 0.93–1.01 (m, 1H, -Si(CH(CH_3)$_2$)$_2$), 1.02 (s, 9H, -C(CH_3)$_3$), 1.25–1.36 (m, 7H, -Si(CH(CH_3)$_2$)$_2$), -Si(CH(CH_3)$_2$)$_2$), 3.87-3.93 (m, 1H, -CHN-), 4.05-4.11 (m, 1H, -CH_2O), 4.22 (s, 5H, C_5H_5), 4.29 (dd, J = 8.5 Hz, 9.9 Hz, -CH_2O), 4.30–4.32 (m, 1H, -C_5H_3), 4.50 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.84 (dd, J = 1.1 Hz, 2.5 Hz, 1H, -C_5H_3), 7.65 (bs, 1H, -OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH), 14.9 (CH), 17.86 (CH_3), 17.94 (CH_3), 18.51 (CH_3), 18.53 (CH_3), 26.5 (CH_3), 33.1 (C), 68.6 (CH_2), 70.3 (CH), 72.0 (C), 72.2 (CH), 72.3 (CH), 73.1 (C), 75.7 (CH), 76.8 (CH), 169.0 (C).

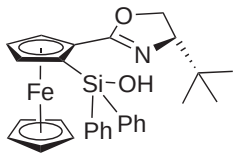
IR (KBr): ν 3444, 2863, 1642, 1149 cm^{-1}.

MS (EI, 70 eV): m/z(%) 441 (M^+, 57), 398 (100), 298 (37).

$[\alpha]_D{}^{25}$ –165.3 (*c* 0.88, $CHCl_3$).

HRMS for $C_{23}H_{35}FeNO_2Si$: calcd. 441.1786, found 441.1786.

4.4.3 Synthesis of (S,R_p)-2-(α-diphenylsilanol)ferrocenyl-5-*tert*-butyloxazoline [(S,R_p)-153c]



It was synthesized according to general procedure C, starting from (S,R_p)-**152c**; 91% yield as an orange solid. Eluent: pentane/diethyl ether = 95/5.

mp. 104 – 105 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 9H, -C(CH_3)$_3$), 3.88 (dd, 1H, J = 9.3 Hz, 10.1 Hz, -CHN), 4.02 (s, 5H, -C_5H_5), 4.14 (t, J = 8.8 Hz, 1H, -CH_2O), 4.24–4.30 (m, 2H, -CH_2O, -C_5H_3), 4.51 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.89 (dd, J = 1.4 Hz, 2.5 Hz, 1H, -C_5H_3), 7.24–7.34 (m, 3H, -Ph), 7.41–7.46 (m, 3H, -Ph), 7.49–7.52 (m, 2H, -Ph), 7.86–7.92 (m, 2H, -Ph), 8.60 (bs, 1H, -OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2 (CH_3), 33.1 (C), 68.6 (CH_2), 70.1 (CH), 70.5 (C), 72.9 (CH), 72.9 (C), 75.1 (CH), 78.1 (CH), 127.3 (CH), 127.4 (CH), 129.0 (CH), 129.5 (CH), 134.4 (CH), 134.7 (CH), 136.0 (C), 138.6 (C), 168.8 (C).

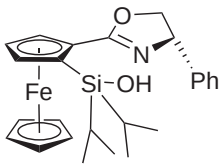
IR (KBr): ν 2955, 1638, 1150, 1113 cm^{-1}.

MS (EI, 70 eV): m/z(%) 509 (M^+, 100).

$[\alpha]_D^{25}$ –446.8 (c 0.5, $CDCl_3$).

Anal. Calcd. for $C_{29}H_{31}FeNO_2Si$: C, 68.36; H, 6.13; N, 2.75; found C, 68.23; H, 6.34; N, 2.56.

4.4.4 Synthesis of (S,R_p)-2-(α-diisopropylsilanol)ferrocenyl-5-phenyloxazoline [(S,R_p)-153d]



It was synthesized according to general procedure C, starting from (S,R_p)-**152d**, in 57% yield as an orange solid. Eluent: pentane/diethyl ether = 80/20.

mp. 99 – 100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (d, J = 7.1 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 0.89 (d, J = 7.1 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 0.93–1.04 (m, 2H, -Si(CH(CH_3)$_2$)$_2$), 1.26–1.30 (m, 3H, -Si(CH(CH_3)$_2$)$_2$), 1.32–1.35 (m, 3H, -Si(CH(CH_3)$_2$)$_2$), 4.20 (t, J = 8.5 Hz, 1H, -CH_2O), 4.26 (s, 5H, -C_5H_5), 4.37 (dd, J = 1.4 Hz, 2.5 Hz, 1H, -C_5H_3), 4.55 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.72 (dd, J = 8.5 Hz, 10.0 Hz, 1H, -CH_2O), 4.92 (dd, J = 1.4 Hz, 2.5 Hz, 1H, -C_5H_3), 5.20–5.28 (m, 1H, -CHN), 7.25–7.42 (m, 5H, -Ph), 7.44 (bs, 1H, -OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH), 14.8 (CH), 17.7 (CH_3), 18.28 (CH_3), 18.33 (CH_3), 68.9 (CH), 70.3 (CH), 72.2 (C), 72.3 (C), 72.4 (CH), 74.4 (CH_2), 77.4 (CH), 126.1 (CH), 127.5 (CH), 128.8 (CH), 141.6 (C), 170.3 (C).

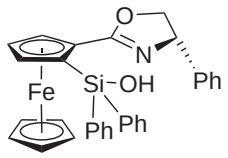
IR (KBr): ν 2940, 2860, 1633, 1148 cm^{-1}.

MS (EI, 70 eV): m/z(%) 461 (M^+, 59), 418 (100).

$[\alpha]_D^{25}$ –227.2 (c 0.5, $CDCl_3$).

Anal. Calcd. for $C_{25}H_{31}FeNO_2Si$: C, 65.07; H, 6.77; N, 3.04; found C, 64.80; H, 6.44; N, 2.86.

4.4.5 Synthesis of (S,R_p)-2-(α-diphenylsilanol)ferrocenyl-5-phenyloxazoline - [(S,R_p)-153e]



It was synthesized according to general procedure C, starting from (S,R_p)-**152e**, in 91% yield as an orange solid. Eluent: pentane/diethyl ether = 95/5.

mp. ≤150 °C (decomp).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.11 (s, 5H, -C_5H_5), 4.18–4.25 (m, 1H, -CH_2O), 4.28–4-30 (m, 1H, -C_5H_3), 4.56 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.62–4.71 (m, 1H, -CH_2O), 4.99–5.01 (m, 1H, -C_5H_3), 5.14–5.24 (m, 1H, -CHN-) 7.25–7.55 (m, 13H, -Ph), 7.82–7.90 (m, 2H, -Ph), 8.26 (bs, 1H, -OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 68.9 (CH), 70.5 (CH), 71.1 (C), 72.6 (C), 73.3 (CH), 73.4 (CH), 74.8 (CH_2), 78.8 (CH), 126.3 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH) 129.1 (CH), 129.4 (CH), 129.8 (CH), 134.7 (CH), 135.0 (CH), 136.0 (C), 138.6 (C), 142.0 (C), 170.5 (C).

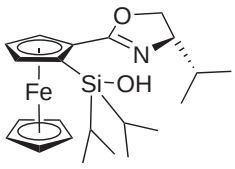
IR (KBr): ν 1626, 1157, 1115 cm^{-1}.

MS (EI, 70 eV): m/z(%) 529 (M^+, 100), 452 (30), 344 (27).

$[\alpha]_D^{25}$ –307.2 (c 0.5, $CDCl_3$).

Anal. Calcd. for $C_{31}H_{27}FeNO_2Si$: C, 70.32; H, 5.14; N, 2.65; found C, 70.09; H, 5.18; N, 2.65.

4.4.6 Synthesis of (S,R_p)-2-(α-diisopropylsilanol)ferrocenyl-5-*iso*-propyloxazoline [(S,R_p)-153f]



It was synthesized according to general procedure C, starting from (S,R_p)-**152f**, in 65% yield as an orange oil. Eluent: pentane/diethyl ether = 85/15.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, J = 7.1 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 0.88 (d, J = 7.1 Hz, 3H, Si(CH(CH_3)$_2$)$_2$), 0.93–0.99 (m, 1H, -Si(CH(CH_3)$_2$)$_2$), 1.00 (d, J = 6.6 Hz, 3H, CH(CH_3)$_2$), 1.19 (d, J = 6.6 Hz, 3H, -CH(CH_3)$_2$), 1.26–1.30 (m, 3H, -Si(CH(CH_3)$_2$)$_2$), 1.32–1.36 (m, 4H, -Si(CH(CH_3)$_2$)$_2$, -Si(CH(CH_3)$_2$)$_2$), 1.76–1.88 (m, 1H, -CH(CH_3)$_2$), 3.90 (dt, J = 6.9 Hz, 9.3 Hz, 1H, -CHN-), 4.03 (t, J =8.5 Hz, 1H, -CH_2O), 4.20 (s, 5H, -C_5H_5), 4.30–4.36 (m, 2H, -C_5H_3, -CH_2O), 4.55 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.84 (dd, J = 1.4 Hz, 2.5 Hz, 1H, -C_5H_3), 7.73 (bs, 1H, -OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (CH), 14.9 (CH), 17.8 (CH_3), 17.9 (CH_3), 18.50 (CH_3), 18.53 (CH_3), 19.1 (CH_3), 19.3 (CH_3), 32.90 (CH), 70.4 (CH_2), 70.5 (CH), 72.0 (CH), 72.28 (CH), 72.30 (CH), 72.9 (C), 77.5 (CH), 168.9 (C).

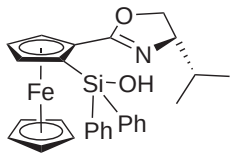
IR (KBr): ν 3098, 2957, 2865, 1643, 1151 cm^{-1}.

MS (EI, 70 eV): m/z(%) 427 (M^+, 47), 384 (100), 298 (25).

$[\alpha]_D^{25}$ –312.1 (c 0.95, $CDCl_3$).

Anal. Calcd. for $C_{22}H_{33}FeNO_2Si$: C, 61.82; H, 7.78; N, 3.28; found C, 61.83; H, 7.92; N, 3.56.

4.4.7 Synthesis of (S,R_p)-2-(α-diphenylsilanol)ferrocenyl-5-*iso*-propyloxazoline [(S,R_p)-153g]



It was synthesized according to general procedure C, starting from (S,R_p)-**152g**, in 82% yield as an orange solid. Eluent: pentane/diethyl ether = 95/5.

mp. 138 – 139 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (d, J = 6.7 Hz, 3H, -CH(CH_3)$_2$), 1.15 (d, J = 6.9 Hz, 3H, -CH(CH_3)$_2$), 1.77–1.90 (m, 1H, -CH(CH_3)$_2$), 3.92 (ddd, J = 6.2 Hz, 8.2 Hz, 9.8 Hz, 1 H, -NCH), 4.03 (s, 5H, -C_5H_5), 4.09 (dd, J = 8.2 Hz, 8.4 Hz, 1H, -CH_2O), 4.28 (dd, J = 1.5 Hz, 2.5 Hz, 1H, -C_5H_3), 4.51 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.90 (dd, J = 1.2 Hz, 2.2 Hz, 1H, -C_5H_3), 7.20–7.35 (m, 3H, -Ph), 7.40–7.55 (m, 3H, -Ph), 7.80–7.85 (m, 2H, -Ph), 8.88 (bs, 1H, -OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 18.8 (CH_3), 18.9 (CH_3), 32.6 (CH), 70.3 (CH_2), 70.4 (CH), 70.7 (C), 71.4 (CH), 73.0 (CH), 73.1 (CH), 78.3 (CH), 127.5 (CH), 127.6 (CH), 129.3 (CH), 129.7 (CH), 134.6 (CH), 134.9 (CH), 136.1 (C), 138.8 (C), 169.1 (C).

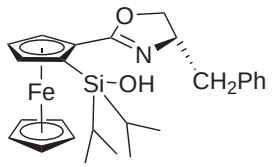
IR (KBr): ν 3048, 2961, 1641, 1155, 1114 cm^{-1}.

MS (EI, 70 eV): m/z(%) 495 (M^+, 100).

$[\alpha]_D{}^{25}$ –393.6 (c 0.5, $CDCl_3$).

Anal. Calcd. for $C_{28}H_{29}FeNO_2Si$: C, 67.88; H, 5.90; N, 2.83; found C, 67.83; H, 6.12; N, 2.60.

4.4.8 Synthesis of (S,R_p)-2-(α-diisopropylsilanol)ferrocenyl-5-benzyloxazoline [(S,R_p)-153h]



It was synthesized according to general procedure C, starting from (S,R_p)-**152h**, in 45% yield as a orange oil. Eluent: pentane/diethyl ether = 95/5.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (d, J = 6.9 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 0.90 (d, J = 6.9 Hz, 3H, -Si(CH(CH_3)$_2$)$_2$), 0.94–1.04 (m, 1H, -Si(CH(CH_3)$_2$)$_2$), 1.26–1.38 (m, 7H, -Si(CH(CH_3)$_2$)$_2$, -Si(CH(CH_3)$_2$)$_2$), 2.79 (dd, J = 9.1 Hz, 13.7 Hz, 1H, -CH_2Ph), 3.24 (dd, J = 4.0 Hz, 13.9 Hz, 1H, -CH_2Ph), 4.08 (t, J = 8.2 Hz, 1H, -CH_2O), 4.15 (s, 5H, -C_5H_5), 4.21–4.28 (m, 1H, -CH_2O), 4.30–4.33 (m, 1H, -C_5H_3), 4.38–4.47 (m, 1H, -CHN), 4.48–4.52 (m, 1H, -C_5H_3), 4.80–4.84 (m, 1H, -C_5H_3), 7.20–7.36 (m, 5H, -Ph), 7.73 (bs, 1H, -OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0. (CH), 15.0 (CH), 17.8 (CH_3), 17.9 (CH_3), 18.49 (CH_3), 18.53 (CH_3), 41.5 (CH_2), 66.8 (CH), 70.6 (CH), 71.3 (CH_2), 72.0 (C), 72.4 (CH), 72.5 (CH), 126. 7 (CH), 128.7 (CH), 129.5 (CH), 137.3 (C), 169.6 (C).

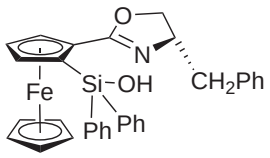
IR (KBr): ν 3090, 2940, 2863, 1640, 1147 cm^{-1}.

MS (EI, 70 eV): m/z(%) 495 (M^+, 54), 432 (100).

$[\alpha]_D^{25}$ –80.8 (c 0.5, $CDCl_3$).

Anal. Calcd. for $C_{26}H_{33}FeNO_2Si$: C, 65.08; H, 7.00; N, 2.95; found C, 64.94; H, 7.08; N, 3.11.

4.4.9 Synthesis of (S,R_p)-2-(α-diphenylsilanol)ferrocenyl-5-benzyloxazoline - [(S,R_p)-153i]



It was synthesized according to general procedure C, starting from (S,R_p)-**152i**, in 43% yield as an orange oil. Eluent: pentane/diethyl ether = 95/5.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85 (dd, J = 8.7 Hz, 13.9 Hz, 1H, -CH_2Ph), 3.21 (dd, J = 4.5 Hz, 13.9 Hz, 1H, -CH_2Ph), 3.97 (s, 5H, -C_5H_5), 4.11 (t, J = 8.2 Hz, 1H, -CH_2O), 4.21–4.28 (m, 2H, -CH_2O, -C_5H_3), 4.35–4.45 (m, 1H, -CHN-), 4.48–4.52 (m, 1H, -C_5H_3), 4.88 (dd, J = 1.2 Hz, 2.2 Hz, 1H, -C_5H_3), 7.20–7.39 (m, 8H, -Ph), 7.41–7.53 (m, 5H, -Ph), 7.86–7.90 (m, 2H, -Ph) 8.62 (bs, 1H, -OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 41.4 (CH_2), 66.5 (CH), 70.5 (CH), 71.4 (CH_2), 72.6 (C), 73.1 (CH), 73.2 (CH), 78.6 (CH), 126.8 (CH), 127.6 (CH), 127.7 (CH), 128.8 (CH), 129.4 (CH), 129.7 (CH), 129.8 (CH), 134.7 (CH), 135.0 (CH), 136.1 (C), 137.3 (C), 138.8 (C), 169.7 (C).

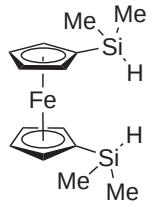
IR (KBr): ν 3008, 2923, 1638, 1151, 1114 cm^{-1}.

MS (EI, 70 eV): m/z(%) 543 (M^+, 100), 466 (28), 344 (24).

$[\alpha]_D^{25}$ –378.0 (c 0.25, $CDCl_3$).

HRMS for $C_{32}H_{29}FeNO_2Si$: calcd. 543.1317, found 543.1317.

4.4.10 Synthesis of 1,1'-bis(dimethylsilyl)ferrocene (158)



To a solution of TMEDA (4.6 mL, 30 mmol) in hexane (20 mL), *n*-BuLi (23 mL, 15% in hexane, 30 mmol) was added dropwise and stirred for 10 min. The resulted mixture was added slowly to a solution of ferrocene (2.5 g, 13.5 mmol) in hexane (100 mL), and stirred at room temperature for 5 h. An orange precipitation formed, and the reaction mixture was cooled to −78 °C on a dry ice/acetone bath, and dimethylchlorosilane (3.3 mL, 30 mmol) was added dropwise. The reaction mixture was stirred for 1 h at the same temperature and after removal of dry ice/acetone bath, the temperature was slowly raised to room temperature, and stirred overnight. Saturated NH_4Cl solution was added and two phase were separated in a separation funnel. Water phase was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic phases was washed with brine (25 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product mixture was separated with flash chromatography using pentan as eluent to separate ferrocene, and to afford desired disilane **158** (2.01 g, 50% yield) as an orange liquid. Eluent: pentane.

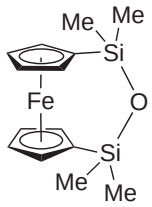
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.31 (d, J = 3.9 Hz, 12H, -Si(CH_3)$_2$), 4.19–4.12 (m, 4H, -C_5H_4), 4.31–4.51 (m, 4H, -C_5H_4), 4.31–4.45 (m, 2H, -SiH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 2.9 (CH_3), 68.2 (C), 71.6 (CH), 73.7 (CH).

MS (EI, 70 eV): m/z(%) 302 (M^+, 100), 285 (60), 243 (32).

Anal. Calcd. for $C_{14}H_{22}FeSi_2$: C, 55.62; H, 7.33. Found: C, 55.62; H, 7.38.

4.4.11 Synthesis of 1,1'-bis(tetramethylsiloxane)ferrocene (159)



To a solution of disilane **158** (122 mg, 0.40 mmol) in acetonitrile (1.5 mL) was added $[RuCl_2(\eta^6\text{-benzene})]_2$ (4 mg, 0.008 mmol) and distilled water (1 drop, ≈ 18 mg, 1 mmol). The reaction mixture was stirred under air for 4 h, and without any work-up, separated with flash chromatography using pentane as eluent to afford disiloxane (60 mg, 48%) and ferrocenyldimethylsilanol (**156**) (52 mg, 47%) as orange crystalline substances. Eluent: pentane/diethyl ether = 90/10.

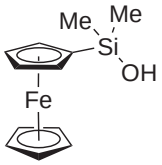
mp. 88 – 89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.30 (s, 12H, -Si(CH_3)$_2$), 4.23–4.25 (m, 4H, -C_5H_4), 4.33–4.53 (m, 4H, -C_5H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ 2.5 (CH_3), 73.0 (C), 73.4 (CH), 75.5 (CH).

MS (EI, 70 eV): m/z(%) 316 (M^+, 100), 281 (52), 237 (12).
Anal. Calcd. for $C_{14}H_{22}FeSi_2O$: C, 53.16; H, 6.37. Found: C, 53.28; H, 6.38.

4.4.12 Synthesis of ferrocenyldimethylsilanol (156)



n-BuLi (0.8 mL of 15% in hexane, 1.3 mmol) was added dropwise to a solution ferrocenyltributyltin (0.48 g, 1.0 mmol) in dry THF (10 mL) at −78 °C. The reaction mixture was stirred for 1.5 h at this temperature and a solution of hexamethyltrisiloxane (70 mg, 0.33 mmol) in THF (6 mL). After removal of dry ice/acetone bath, the temperature was slowly raised to room temperature, and it was stirred overnight, water (15 mL) was added, extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, concentrated under vacuum, separated by column chromatography using pentane/diethyl ether (95/5) as eluent to afford silanol **156** (0.131 g, 44%) as an orange solid. Eluent: pentane/diethyl ether = 85/15.

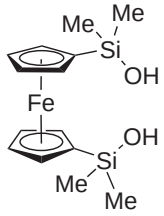
mp. 63 − 65 °C. Lit [207]: 62 − 63 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.39 (s, 6H, -Si(CH_3)$_2$), 1.79 (bs, 1H, -OH), 4.15 (s, 5H, -C_5H_5), 4.16–4.18 (m, 2H, -C_5H_3), 4.37–4.39 (m, 2H, -C_5H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 0.5 (CH_3), 67.9 (CH), 69.8 (C), 70.8 (CH), 72.4 (CH).

MS (EI, 70 eV): m/z(%) 260 (M^+, 100), 245 (71), 179 (14).

4.4.13 Synthesis of 1,1'-bis(dimethylsilanol)ferrocene (160)



***via* 1'-Lithiation of ferrocenyldimethylsilanol (156)**

To a solution of ferrocenyldimethylsilanol (**156**) (65 mg, 0.25 mmol) in dry THF (0.4 mL) under inert atmosphere at room temperature, *t*-BuLi (0.4 mL of 15% in hexane, 0.6 mmol) was added dropwise. The resultion solution was refluxed for 18 hours and after cooling to room temperature, DMF (0.04 mL, 0.6 mmol) was added. After 24 hours stirring at room temperature, water was added (1 mL) and extracted with diethyl ether (3 x 2 mL). Organic phases were collected, dried over $MgSO_4$ and concentrated under vacuum. The crude product mixture was purified by flash chromatography using pentan/diethylether (85/15) as eluent to afford disilanol **160** (16 mg, 19% yield) as an orange liquid.

***via* 1,1'-Dilithiation of ferrocene**

To a solution of TMEDA (4.6 mL, 30 mmol) in hexane (20 mL), *n*-BuLi (23 mL, 15% in hexane, 30 mmol) was added dropwise and stirred for 10 min. The resulted mixture was added slowly to a solution of ferrocene (2.5 g, 13.5 mmol) in hexane (100 mL), and stirred at room temperature for 5 h. An orange precipitate formed, and the reaction mixture was cooled to -78 °C on a dry ice/acetone bath, and hexamethyltrisiloxane (2.0 g, 9.0 mmol) was added dropwise. The reaction mixture was stirred for 1 h at the same temperature and after removal of dry ice/acetone bath, the temperature was slowly raised to room temperature, and stirred overnight. Saturated NH_4Cl solution was added and two phase were separated in a separation funnel. Water phase was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic phases were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product mixture was separated with flash chromatography using pentan as eluent to separate ferrocene, and to afford desired disilanol **156** (1.06 g, 23% yield) as an orange solid.

mp. 130 – 131 °C.

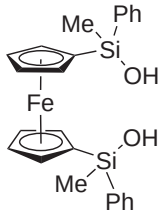
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.32 (s, 12H, -Si(CH_3)$_2$), 4.22 (t, J = 1.7 Hz, 4H, -C_5H_4), 4.37 (t, J = 1.7 Hz, 4H, -C_5H_4), 5.54 (bs, 2H, -SiOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 1.8 (CH_3), 70.5 (C), 71.0 (CH), 73.4 (CH).

MS (EI, 70 eV): m/z(%) 334 (M^+, 100), 317 (25), 149 (20).

Anal. Calcd. for $C_{14}H_{22}FeO_2Si_2$: C, 50.29; H, 6.63. Found: C, 50.45; H, 6.62.

4.4.14 Synthesis of *rac*-1,1'-bis(phenylmethylsilanol)ferrocene (161)



It was synthesized applying the same procedure as for the synthesis of disilanol **160**, starting from the same amount of ferrocene (2.5g, 13.5 mmol) and using triphenyl-trimethyl-trisilaxone (3.7 mL, 9 mmol) as an electrophile to afford chiral disilanol **161** (1.03 g, 16% yield) as an orange solid.

mp. 127 – 129 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.55 (s, 6H, -$SiCH_3$), 4.13–4.21 (m, 4H, -C_5H_4), 4.30–4.37 (m, 4H, -C_5H_4), 6.29 (bs, 2H, -SiOH), 7.26–7.40 (m, 6H, -Ph), 7.57–7.63 (m, 4H, -Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ 1.3 (CH_3), 69.9 (C), 72.2 (CH), 72.4 (CH), 74.6 (CH), 75.2 (CH), 128.7 (CH), 130.4 (CH), 134.4 (CH), 139.2 (C).

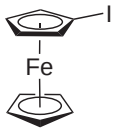
MS (EI, 70 eV): m/z(%) 458 (M^+, 100), 440 (27), 322 (18).

IR (KBr): ν 3067, 2957, 1425, 1254, 1166, 1036 cm^{-1}.

Anal. Calcd. for $C_{24}H_{26}FeO_2Si_2$: C, 62.87; H, 5.72. Found: C, 63.14; H, 6.06.

4.5 Synthesis of *N*-Substituted Ferrocenes

4.5.1 Synthesis of Iodoferrocene (193)



It has been synthesized according to following slightly modified Kagan's procedure. [156] Iodine (1.4 g, 5.5 mmol) was added to the solution of ferrocenyltributyltin[1](2.38 g, 5.0 mmol) in 20 mL of CH_2Cl_2 at room temperature under inert atmosphere. The reaction mixture was stirred at room temperature for 24 h. Excess iodine was removed by washing with saturated $Na_2S_2O_3$ solution, and filtered through neutral Al_2O_3, and the solvent was evaporated. The crude product mixture was dissolved in MeOH (10 mL), KF (1 g) was added to precipicate the stannylated byproducts which were removed by filtration through neutral Al_2O_3. The product was diluted with diethylether (15ml) and washed with water (15 mL), and dried over $MgSO_4$, and concentrated under vakuum. Finally, it is one more filtrated, this time through silica gel using pentan as eluent and after recrystallisation with hexane, product (0.66 g, 42% yield) was obtained as red-brown crystals. which can be stored in dark at low temperature (-24 °C) for a long time without decomposition.

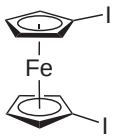
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15–4.16 (m, 2H, -C_5H_4), 4.15 (s, 5H, -C_5H_5), 4.40–4.42 (m, 2H, -C_5H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ 68.9 (CH), 71.1 (CH), 74.5 (CH).

MS (EI, 70 eV): m/z(%) 312 (M^+, 100), 184 (27), 129 (21).

[1]It is prepared according to the Kagan's procedure [156]

4.5.2 Synthesis of 1,1'-diiodoferrocene (196)



To a solution of TMEDA (4.6 mL, 30 mmol) in hexane (20 mL), *n*-BuLi (23 mL of 15% in hexane, 30 mmol) was added slowly and stirred for 10 min. The resulted mixture was added slowly to a solution of ferrocene (2.5 g, 13.5 mmol) in hexane (100 mL), and stirred at room temperature for 5 h. An orange precipitate formed, and the reaction mixture was cooled to −78 °C on a dry ice/acetone bath, and a solution of iodine (10.6 g, 30 mmol) in diethylether (75 mL) was added slowly within 15 min. The reaction mixture stirred for 1 h at the same temperature and after removal of dry ice/acetone bath, the temperature was slowly raised to 0 °C, and water (25 mL) was added. After stirring for 15 min, the mixture was filtrated and the two phase were separated in a separation funnel. The organic phase was washed with saturated $Na_2S_2O_3$ solution (25 mL) and water (2 x 50 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product mixture was first separated over a short column filled with neutral Al_2O_3 using pentane as eluent and then with a very long column filled with silica gel[2] using pentane as eluent to separate iodoferrocene, and to afford diiodoferrocene (0.64 g, 11% yield) as a dark-orange oil.[3]

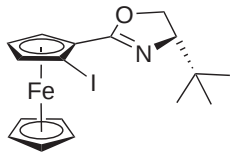
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18–4.21 (m, 4H, -C_5H_4), 4.38–4.41 (m, 4H, -C_5H_4).

^{13}C NMR (75 MHz, $CDCl_3$): δ 72.3 (CH), 77.6 (CH).

MS (EI, 70 eV): m/z(%) 438 (M^+, 100), 311 (9), 183 (11), 128 (31).

[2]It was found that silica gel gave a better separation than alumina
[3]Spectroscopical data is consistent with literature data: [208]

4.5.3 Synthesis of (S,R_p)-α-iodo-ferrocenyl-5-benzyloxazoline [(S,R_p)-211]



To a solution of ferrocenyl oxazoline **74** (0.311 g, 1.0 mmol) in dry THF (20 mL) at −78 °C under inert atmosphere, *sec*-BuLi (1.0 mL of 1.3 M in cyclohexane, 1.3 mmol) was added slowly, and resulting red solution was stirred for 2 h. Solid iodine (0.354 g, 1.0 mmol) was added at once to the solution, and it was stirred overnight. Excess amount of iodine was removed by washing with saturated $Na_2S_2O_3$ solution (20 mL) and extracted with diethylether (2 x 20 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum to obtain crude product. It was, then, separated with flash chromatography to obtain iodooxazoline **211**(0.381 g, 87%) as a dark orange solid.[4]

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 9H, -C($(CH_3)_3$), 3.98 (dd, J = 7.3 Hz, 8.5 Hz, 1H, -CHN), 4.18–4.26 (m, 2H, -CH_2O), 4.20 (s, 5H, -C_5H_5), 4.36 (t, J = 2.5 Hz, 1H, -C_5H_3), 4.62 (dd, J = 1.4 Hz, 2.5 Hz, 1H, -C_5H_3), 4.69 (bs, 1H, -C_5H_3).

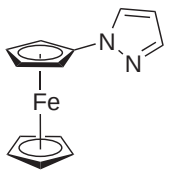
^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0 (CH_3), 34.0 (C), 38.7 (C), 68.1 (CH_2), 69.6 (CH), 70.9 (CH), 72.6 (CH), 76.5 (CH), 78.4 (CH).

[4]It is a slightly modified version of Bolm's procedures and spectroscopical data is consistent with literature data: [200]

4.5.4 Synthesis of *N*-substituted ferrocenes; General Procedure D

Iodoferrocene (62.5 mg, 0.20 mmol), the nitrogen-containing coupling partner (R-[N]-H, 0.22 mmol), copper(I) iodide (38 mg, 0.2 mmol) and the base (0.4 mmol) were added into dry DMSO (0.4 mL) under Ar atmosphere. A slurry mixture was formed, which was heated to 90 °C for 18 h. After cooling to room temperature, water (2.0 mL) and diethyl ether (2 mL) were added. Then, the organic phase was separated and the aqueous phase extracted with diethyl ether until no colorful organic phase was visible anymore. The combined organic phases were dried over $MgSO_4$, filtered and the solvent evaporated to give the crude product. Purification by flash column chromatography (pentane/diethyl ether = 1/9) afforded the product.

4.5.5 Synthesis of *N*-ferrocenyl pyrazole (93)



It was synthesized (42 mg, 84%) according to general procedure D, using pyrazole (15 mg, 0.22 mmol) as coupling component and K_2CO_3 (56 mg, 0.40 mmol) as base in 84% yield as an orange crystalline substance (42 mg).
mp. 119 − 120 °C.

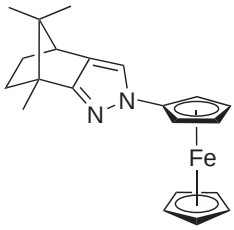
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17 (s, 5H, -C_5H_5), 4.16–4.17 (m, 2H, -C_5H_4) 4.76 (t, J = 1.9 Hz, 2H, -C_5H_4), 6.32–6.33 (m, 1H, -CH), 7.62 (d, J = 1.4 Hz, 1H, -NCH), 7.67 (d, J = 2.5 Hz, 1H, -NCH) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 60.8 (CH), 65.8 (CH), 69.8 (CH), 98.2 (C), 106.5 (CH), 128.1 (CH), 140.0 (CH) ppm.

IR (KBr): ν 3090, 1529, 1393, 1004, 873, 825, 759, 499 cm^{-1}.

MS (EI, 70 eV): m/z(%) 252 (M^+, 100), 187 (14), 131 (19), 56 (8).

Anal. Calcd. for $C_{13}H_{12}FeN_2$: C, 61.94; H, 4.80; N, 11.11. Found: C, 61.67; H, 4.97; N, 11.04.

4.5.6 Synthesis of *N*-ferrocenyl-(4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazole (95)



It was synthesized according to general procedure D, using chiralpyrazole (194 mg, 1.1 mmol) as coupling component and K_2CO_3 (560 mg, 4.0 mmol) as base in 71% yield as an orange solid (254 mg).

mp. 136 – 138 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72 (s, 3H, -C(CH_3)$_2$), 0.97 (s, 3H, -C(CH_3)$_2$), 1.15–1.24 (m, 1H, -CH_2), 1.33 (s, 3H, -CH_3) 1.34–1.42 (m, 1H, -CH_2), 1.85 (ddd, J = 4.0 Hz, 10.1 Hz, 12.1 Hz, 1H, -CH_2), 2.08 (ddt, J = 4.0 Hz, 9.9 Hz, 11.9 Hz, 1H, -CH_2), 2.76 (d, J = 4.0 Hz, 1H, -CH), 4.07–4.10 (m, 2H, –C_5H_4), 4.13 (s, 5H, -C_5H_5), 4.64 (dt, J = 1.5 Hz, 2.2 Hz, 1H, -C_5H_4), 4.71 (dt, J = 1.5 Hz, 2.2 Hz, 1H, -C_5H_4), 7.21 (s, 1H, -NCH).

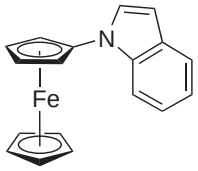
^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8 (CH_3), 19.1 (CH_3), 20.6 (CH_3), 27.7 (CH_2), 33.7 (CH_2), 47.2 (CH), 50.4 (C), 59.9 (CH), 60.2 (CH), 60.4 (C) 65.0 (CH), 65.1 (CH), 69.5 (CH), 120.2 (CH), 128.1 (C), 167.1 (C).

MS (EI, 70 eV): m/z(%) 360 (M^+, 100), 358 (7), 345 (5), 317 (19), 251 (6), 195 (4), 121 (4).

Anal. Calcd. for $C_{21}H_{24}FeN_2$: C, 70.01; H, 6.71; N, 7.78. Found: C, 70.00; H, 6.60; N, 7.72.

$[\alpha]_D^{25}$ –13.6 (c 0.43, $CDCl_3$).

4.5.7 Synthesis of *N*-ferrocenyl indole (199)



It was synthesized according to general procedure D, using indole (15 mg, 0.22 mmol) as coupling component and K_2CO_3 (56 mg, 0.40 mmol) as base in 73% yield as an orange solid (44 mg).

mp. 89 – 91 °C. Lit [209]: 89 – 90 °C.

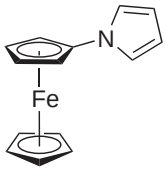
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20-4.22 (m, 2H, -C_5H_4), 4.23 (s, 5H, -C_5H_5), 4.62–4.64 (m, 2H, -C_5H_4), 6.57 (d, J = 3.2 Hz, 1H, -NCH), 7.10–7.17 (m, 1H, -C_6H_4), 7.20–7.27 (m, 1H, -C_6H_4), 7.40 (d, J = 3.2 Hz, 1H, -CH), 7.63 (dd, J = 0.7 Hz, 7.7 Hz, 1H, -C_6H_4), 7.73 (dd, J = 0.7 Hz, 8.2 Hz, 1H, -C_6H_4).

^{13}C NMR (75 MHz, $CDCl_3$): δ 62.8 (CH), 65.4 (CH), 69.4 (CH), 97.4 (C), 102.8 (CH), 111.3 (CH), 120.1 (CH), 121.1 (CH), 122.0 (CH), 129.3 (C), 136.7 (C).

IR (KBr): ν 1521, 1446, 1311, 1234, 1141, 1103, 815, 740, 499 cm^{-1}.

MS (EI, 70 eV): m/z(%) 301 (M^+, 100), 235 (5), 180 (5), 150 (3).

4.5.8 Synthesis of *N*-ferrocenyl pyrrole (200)



It was synthesized according to general procedure D, using pyrrole (15 mg, 0.22 mmol) as coupling component and K_2CO_3 (56 mg, 0.40 mmol) as base in 62% yield as an orange solid (31 mg).

mp. 80 – 81 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.03 (t, J = 2.0 Hz, 2H, -C_5H_4), 4.10 (s, 5H, -C_5H_5), 4.44 (t, J = 2.0 Hz, 2H, -C_5H_4), 6.12–6.14 (m, 2H, -NCH), 6.85–6.87 (m, 2H, -CH).

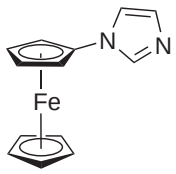
^{13}C NMR (75 MHz, $CDCl_3$): δ 61.1 (CH), 65.3 (CH), 69.6 (CH), 63.8 (CH), 109.1 (CH), 120.8 (CH).

IR (KBr): ν 3106, 1527, 1302, 1080 cm^{-1}.

MS (EI, 70 eV): m/z(%) 251 (M^+, 100), 185 (9), 130 (5).

Anal. Calcd. for $C_{14}H_{13}FeN$: C, 66.96; H, 5.22; N, 5.58. Found: C, 66.95; H, 5.26; N, 5.34

4.5.9 Synthsis of *N*-ferrocenyl imidazole



It was synthesized according to general procedure D, using imidazole (15 mg, 0.22 mmol) as coupling component and K_2CO_3 (56 mg, 0.40 mmol) as base, with a longer reaction time (36 h), in 33% yield as an orange crystalline substance (20 mg).

mp. 100 – 101 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 (t, J = 1.9 Hz, 2H, -C_5H_4), 4.21 (s, 5H, -C_5H_5), 4.54 (t, J = 1.9 Hz, 2H, -C_5H_4), 7.10 (bs, 1H, -NCH), 7.17 (bs, 1H, -NCH), 7.74 (bs, 1H, -NCHN).

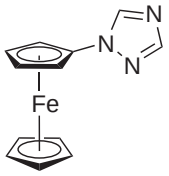
^{13}C NMR (100 MHz, $CDCl_3$): δ 62.1 (CH), 66.1 (CH), 69.9 (CH).

IR (KBr): ν 3083, 1528, 1247, 1104, 1034 cm^{-1}.

MS (EI, 70 eV): m/z(%) 252 (M^+, 100), 187 (34), 121 (8), 56 (6).

HRMS for $C_{13}H_{12}FeN_2$: calcd. 252.0349, found 252.0349.

4.5.10 Synthesis of 1-ferrocenyl-1,2,4-triazole (202)



It was synthesized according to general procedure D, using triazole (15 mg, 0.22 mmol) as coupling component and KO*t*-Bu (45 mg, 0.40 mmol) as base in 30% yield as an orange crystalline substance (15 mg).

mp. 107 – 109 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (s, 5H, -C_5H_5), 4.25 (t, J = 1.9 Hz, 2H, -C_5H_4), 4.76 (t, J = 2.0 Hz, 2H, -C_5H_4), 8.01 (s, 1H, -NCH), 8.32 (s, 1H, -NCH).

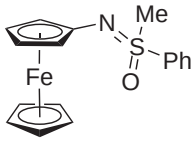
^{13}C NMR (75 MHz, $CDCl_3$): δ 61.6 (CH), 66.3 (CH), 69.9 (CH), 77.1 (C), 151.9 (CH).

IR (KBr): ν 3872, 3425, 1632, 1529, 1273, 1100, 1018 cm^{-1}.

MS (EI, 70 eV): m/z(%) 253 (M^+, 100), 199 (19), 121 (11).

HRMS for $C_{12}H_{11}FeN_3$: cald. 253.0302, found 253.0302.

4.5.11 Synthesis of *N*-ferrocenyl-methyl phenyl sulfoximine (203)



It was synthesized according to general procedure D using sulfoximine **191** (34 mg, 0.22

mmol) as coupling component and K_2CO_3 (56 mg, 0.40 mmol) as base in 80% yield as an orange crystalline substance (54 mg).

mp. 92 – 94 °C.

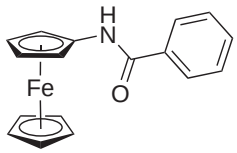
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.17 (s, 3H, -CH_3), 3.77–3.80 (m, 1H, C_5H_4), 3.80–3.85 (m, 1H, -C_5H_4), 3.88–3.91 (m, 1H, -C_5H_4), 4.03–4.07 (m, 1H, -C_5H_4), 4.11 (s, 5H, -C_5H_5), 7.51–7.65 (m, 3H, -Ph), 7.91–7.96 (m, 2H, -Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ 46.0 (CH_3), 61.5 (CH), 62.6 (CH), 63.8 (CH), 69.3 (CH), 128.5 (CH), 129.6 (CH), 133.2 (CH), 140.0 (C).

MS (EI, 70 eV): m/z(%) 339 (M^+, 100), 199 (35), 133 (11).

Anal. Calcd. for $C_{17}H_{17}FeNOS$: C, 60.19; H, 5.05; N, 4.13. Found: C, 59.84; H, 5.12; N, 4.06.

4.5.12 Synthesis of *N*-ferrocenyl-benzamide (205)



It was synthesized according to general procedure D, using benzamide (27 mg, 0.22 mmol) as coupling component and KO*t*-Bu (45 mg, 0.40 mmol) as base in 57% yield as an orange solid (35 mg).

mp. 179 – 181 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (bs, 2H, -C_5H_4), 4.21 (s, 5H, -C_5H_5), 4.77 (bs, 2H, -C_5H_4), 7.30 (bs, 1H, -NH), 7.43–7.55 (m, 3H, -C_6H_5), 7.80–7.82 (m, 2H, -C_6H_5).

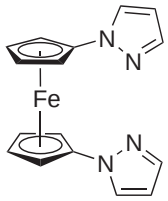
^{13}C NMR (100 MHz, $CDCl_3$): δ 61.7 (CH), 64.9 (CH), 69.5 (CH), 126.8 (CH), 128.7 (CH), 131.6 (CH), 134.7 (C), 165.4 (C).

IR (KBr): ν 3304, 3091, 1643, 1556, 1281, 1000 cm^{-1}.

MS (EI, 70 eV): *m/z*(%) 305 (M^+, 100), 240 (43), 202 (7), 185 (7), 121 (9).

Anal. Calcd. for $C_{17}H_{15}FeNO$: C, 66.91; H, 4.95; N, 4.59. Found: C, 67.24; H, 5.21; N, 4.59.

4.5.13 Synthesis of 1,1'-bis(*N*-pyrazolyl) ferrocene (208)



It was synthesized according to general procedure D, using pyrazole (30 mg, 0.44 mmol) as coupling component and K_2CO_3 (56 mg, 0.40 mmol) as base in 50% yield as an orange solid (40 mg).

mp. $154 - 156$ °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (t, J = 1.7 Hz, 4H, -C_5H_4), 4.71 (t, J = 1.7 Hz, 4H, -C_5H_4), 6.26 (t, J = 1.7 Hz, 2H, -CH), 7.49 (d, J = 2.2 Hz, 2H, -NCH), 7.55 (d, J = 2.2 Hz, 2H, -NCH).

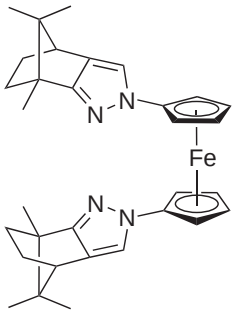
^{13}C NMR (75 MHz, $CDCl_3$): δ 61.9 (CH), 67.1 (CH), 99.2 (C), 106.6 (CH), 128.1 (CH), 140.2 (CH).

IR (KBr): ν 1534, 1393, 869, 811, 742, 511 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) 318 (M^+, 100), 187 (7), 159 (4), 131 (6).

HRMS calcd for $C_{16}H_{14}FeN_4$: calcd. 318.0568, found 318.0568.

4.5.14 Synthesis of 1,1'-bis[(4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl] ferrocene (209)



It was synthesized according to general procedure D, using chiral pyrazole **197** (77 mg, 0.44 mmol) as coupling component and K_2CO_3 (56 mg, 0.40 mmol) as base in 30% yield as an orange solid (33 mg).

mp. decomp $\leq$ 160 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73 (s, 6H, -C(CH_3)$_2$), 0.97 (s, 6H, -(CH_3)$_2$), 1.17–1.28 (m, 4H, -CH_2), 1.33 (s, 6H, -CH_3), 1.34–1.41 (m, 2H, -CH_2), 1.86 (ddd, J = 3.8 Hz, 10.2 Hz, 12.2 Hz, 2H, -CH_2), 2.09 (ddt, J = 3.8 Hz, 10.1 Hz, 12.1 Hz, 2H, -CH_2), 2.75 (d, J =3.8 Hz, 2H, -CH), 4.08 (dt, J = 1.4 Hz, 2.5 Hz, 2H, -C_5H_4), 4.10 (dt, J = 1.4 Hz, 2.5 Hz, 2H, -C_5H_4), 4.49–4.52 (m, 2H, -C_5H_4), 4.53–4.56 (m, 2H, -C_5H_4), 7.13 (s, 2H, -NCH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0 (CH_3), 19.3 (CH_3), 20.7 (CH_3), 27.8 (CH_2), 33.8 (CH_2), 47.3 (CH), 50.5 (C), 60.4 (C), 61.6 (CH), 62.0 (CH), 66.6 (CH), 100.4 (C), 120.6 (CH), 128.1 (C), 167.2 (C).

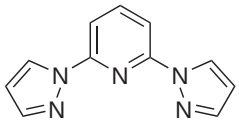
IR (KBr): ν 1591, 1525, 1405, 1382, 1286, 499 cm^{-1}.

MS (EI, 70 eV): m/z(%) 534 (M^+, 100).

HRMS for $C_{32}H_{38}FeN_4$: calcd. 534.2446, found 534.2447.

$[\alpha]_D{}^{25}$ +63.1 (c 0.65, $CDCl_3$).

4.5.15 Synthesis of 2,6-bis(*N*-pyrazolyl)pyridine (220)

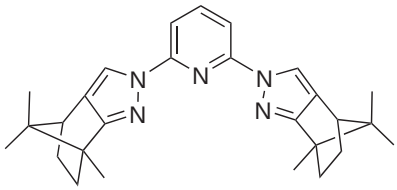


It was synthesized according to general procedure D, using 2,6-dibromopyridine (47 mg, 0.20 mmol), pyrazole (30 mg, 0.44 mmol) as coupling component and K_2CO_3 (56 mg, 0.40 mmol) as base in 72% yield as a white crystalline compound (33 mg). Spectroscopical data is consistent with literature data. [201]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (dd, J = 1.6 Hz, 2.5 Hz, 2H, -CHC), 7.75–7.77 (m, 2H, -CHN), 7.83–7.86 (m, 2H, -CHC), 7.91–7.95 (m, 1H, -CHC), 8.57 (d, J = 2.8 Hz, -CHN).

^{13}C NMR (100 MHz, $CDCl_3$): δ 108.0 (CH), 109.4 (CH), 127.0 (CH), 141.4 (CH), 142.3 (CH), 150.0 (C).

4.5.16 Synthesis of 2,6-bis[(4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl]pyridine (221)



It was synthesized according to general procedure D, using 2,6-dibromopyridine (47 mg, 0.20 mmol), chiral pyrazole **197** (77 mg, 0.44 mmol) as coupling component and K_2CO_3 (56 mg, 0.40 mmol) as base in 47% yield as a white crystalline compound (49 mg). Spectroscopical data is consistent with literature data. [203]

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (s, 6H, -C(CH_3)$_2$)), 1.00 (s, 6H, -C(CH_3)$_2$)), 1.20–1.31 (m, 2H, -CH_2), 1.34 (s, 6H, -C(CH_3)$_2$)), 1.38–1.48 (m, 2H, -CH_2), 1.90 (ddd, J = 3.7 Hz, 10.1 Hz, 12.2 Hz, 2H, -CH_2), 2.12 (ddt, J = 4.0 Hz, 9.9 Hz, 11.9 Hz, 2H, -CH_2), 2.82 (d, J = 4.0 Hz, -CH), 7.55–7.58 (m, 2H, -CH), 7.74 (dd, J = 7.4 Hz, 8.8 Hz, 1H, -CH), 8.10 (s, 2H, -CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 (CH_3), 19.0 (CH_3), 20.7 (CH_3), 27.6 (CH_2), 33.7 (CH_2), 47.0 (CH), 50.3 (C), 60.0 (C), 106.8 (CH), 118.5 (CH), 129.2 (C), 140.5 (C), 150.8 (CH), 169.9 (CH).

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Chapter 5

Appendix

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5.2 Curriculum Vitae

Personal data

Name: Salih Özçubukçu

Date of birth: 15.03.1980

Place of birth: Gaziantep

Nationality: Turkish

Education

1992–1998, Izmir Private Yamanlar High School (Izmir/Turkey) GPA : 5.00/5.00 ranking 1^{st}

1998–2002, Middle East Technical University (Ankara/Turkey)

B.A. in Chemistry, GPA : 3.70/4.00 ranking 1^{st}

January 2002–September 2002, Middle East Technical University (Ankara/Turkey)

M.Sc. in Organic Chemistry, GPA : 3.94/4.00

Awards

1995, International Chemistry Olympiad, China, Bronze Medal

1996, International Chemistry Olympiad, Russia, Silver Medal

1997, International Chemistry Olympiad, Canada, Gold Medal

Ranking 1^{st} in ca. 200 selected students over 55 countries.

1994, 1995, 1996, 1997, National Chemistry Olympiads one Bronze, one Silver and two Gold Medals, respectively.

Research Experience

June - September 2001, Research Study and Summer Practice about Asymmetric Synthesis in Institute of Organic Chemistry RWTH Aachen, Germany under the supervision of Prof. Bolm

March - April 2005, Assistance in General Chemistry Laboratory

September 2005 - February 2006, Assistance in Advanced Organic Chemistry Laboratory.

February - May 2006, Research Study on 'Au(I)-catalyzed cycloisomerization reactions' in University of California, Berkeley under the supervision of Prof. F. Dean Toste.

January 2003 - January 2007, Ph.D. studies at the Institute for Organic Chemistry, RWTH-Aachen University, Germany under the supervision of Prof. Bolm.