Multidentate Di-N-heterocyclic carbene ligands for transition metal catalyzed hydrogenation reactions
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Citation for published version (APA):

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Chapter 1
Introduction: Bidentate (di-)NHC Ligands bearing tzNHCs in Organometallic Chemistry and Homogeneous Catalysis
1.1 Organometallic Chemistry and Homogeneous Catalysis

Catalysis is essential to life on our planet. Enzymes, nature’s catalysts, enable chemical reactions in bio-systems, thereby making life possible in the first place. Moreover, catalysts are used in most industrial processes (>80%).\(^1\) Herein they facilitate the production of chemicals for various applications and products for everyday life, ranging from plastics and the fuel in our cars to pharmaceuticals. Catalysts can increase the rate at which reactions proceed. More importantly, they can prevent side reactions, making transformations more selective, which leads to fewer byproducts and less waste. To achieve a more sustainable chemical industry, much research in industry as well as academia is nowadays devoted to developing and improving catalytic systems. The research described in this thesis is a contribution to this end in the field of homogeneous catalysis.

In homogeneous catalysis the catalysts influence the rate and outcome of a reaction while being in the same phase as the reaction (usually in solution). Often they are organometallic compounds consisting of a (transition) metal surrounded by organic molecules, the ligands. These ligands influence the properties of the metal catalyst. Optimization of the steric and electronic characteristics of the ligands and their coordination to a suitable metal is therefore key to the performance of a catalyst. The accumulated knowledge on ligands and organometallic catalysts is extensive, including understanding of the mechanisms of catalytic reactions as well as the effects of certain ligand parameters. This makes it possible to design homogeneous catalysts in a rational manner. Traditional ligands in homogeneous catalysis were mostly based on oxygen, nitrogen, sulfur or phosphorus donor atoms, binding through a lone-pair on the atom. More recently, N-heterocyclic carbenes (NHCs), the class of ligands employed throughout this thesis, have been established as viable ligands.

1.2 N-heterocyclic Carbene Ligands

Nowadays, NHCs are paramount to organometallic chemistry and homogeneous catalysis.\(^2-4\) NHCs consist of a singlet carbene in a heterocyclic ring. The \(\text{sp}^2\)-hybridized carbon has a lone pair available for donation to the metal center of choice. Although free carbenes are very reactive, some can be isolated. Arduengo was the first to achieve this for a bulky imidazol-2-ylidene in the 1990’s (Figure 1).\(^5\) Hence, these most well-known NHCs are also called Arduengo-type carbenes. The reactive carbene center was reasoned to be stabilized by steric shielding of the bulky side groups. The steric bulk can, for example, prevent the NHC from dimerization.

Additionally, NHCs derive their relative stability from their structure having a “push-and-pull” system (Figure 1). The two nitrogen atoms adjacent to the carbene carbon donate electron-density from their lone pairs into the empty \(p\)-orbital of...
the carbene (“push”). This causes the filled lone pair orbital, orthogonal to the stabilizing π-system, to be available for σ-donation. Besides, the nitrogen atoms also have a inductive mildly electron-withdrawing (“pull”) effect.

![Figure 1: Stabilization of the carbene moiety in NHCs; sterically in case of Arduengo’s bis-adamantyl-NHC (left) and electronically by the “push-and-pull” effect (right).](image)

The first NHC metal complexes were reported by Öfele and Wanzlick in 1968. Since then, they have been coordinated to almost every metal in the periodic table. In the early days, NHCs were viewed as simple σ-donors, donating electron-density in an empty d-orbital of the metal. However, for the binding with electron-rich transition metals (TM) NHCs also accept electron-density in the π* orbital. The important orbital interactions that constitute the M-NHC bond are depicted in Figure 2.

![Figure 2: Schematic representation of the relevant molecular orbital interactions constituting the M-NHC bond, left: imidazol-2-ylidene and right: 1,2,3-triazolylidene.](image)
Several ways of making metal NHCs are known and a selection is depicted in Scheme 1.\textsuperscript{11} As most free NHCs are not shelf-stable, their metal complexes are mostly prepared via deprotonation of the corresponding imidazolium salts in the presence of the appropriate metal precursor. Various strong bases (at low temperatures) as well as internal bases at the metal precursor have been used to deprotonate the NHC precursors.\textsuperscript{12} Another popular synthetic route is transmetalation. Here, the imidazolium salt is coordinated to a metal, usually silver(I), that can subsequently transfer the carbene to a second metal center.\textsuperscript{13,14} Additionally, a metal can be inserted in the C=C bond of the Wanzlick carbene dimer,\textsuperscript{15} and oxidative addition of a C-X bond (e.g., X = halide, alkyl, H) can lead to an NHC-M complex.\textsuperscript{16–19} Lastly, the group of Hahn developed an entirely different approach. They obtained (asymmetrically substituted) saturated or benzimidazolylidene complexes by intramolecular cyclization (via nucleophilic attack of an amine to a functionalized isonitrile) on the metal center.\textsuperscript{20,21}

\textbf{Scheme 1:} Upper part: Synthetic routes to prepare NHC-M complexes: direct deprotonation, transmetalation via the Ag(I) complex, metal insertion in C-X or C=C bond and cyclization of isonitrile complex. Lower part: Fields in which they are applied.

NHC metal complexes have been applied in medicinal chemistry,\textsuperscript{22} material science (photoluminescence)\textsuperscript{23} and organocatalysis,\textsuperscript{24} but above all in homogeneous transition metal catalysis (Scheme 1).\textsuperscript{8,25} One of the most well-known NHC
catalysts is Grubbs’ second generation olefin metathesis catalyst. In this catalytic system the impact of the enhanced $\sigma$-donating properties is nicely illustrated. The replacement of one of the two tricyclohexylphosphine ligands in Grubbs’ first generation catalyst\textsuperscript{26} with an NHC\textsuperscript{27} leads to an enhanced catalytic rate by a factor of $10^2$-$10^3$ (Scheme 2).\textsuperscript{28,29} This rate enhancement is attributed to the weakened M-P bond; the increase in electron-density on the metal caused by the NHC ligand labilizes the metal-phosphine bond, facilitating dissociation of the phosphine ligand, which is necessary for the complex to enter the catalytic cycle.

![Scheme 2: Grubbs’ first and second generation metathesis catalyst and dissociation of one PCy$_3$ leading to the active catalyst. This step is significantly faster when the phosphine ligand is replaced by an NHC (Grubbs II) with highly increased activity as a result. Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.](image)

**Triazole-based mesoionic carbene ligands**

Next to imidazole-2-ylidenes, several other types of NHCs have been developed in the last decade (Figure 3). The electron-donating properties of these NHCs are influenced to a large extent by the position of the nitrogen atoms in the ring.

![Figure 3: Several NHCs arranged by increasing $\sigma$-donor properties according to their TEP (Tolman Electronic Parameter = $v_{CO}$ of [Ni(CO)$_3$(NHC)]) data: phosphines, 1,2,4-triazolylidene, saturated imidazole-2-ylidene, imidazole-2-ylidene, six-membered expanded ring NHC, 1,2,3-triazolylidene, imidazole-4-ylidene and pyrazolin-4-ylidene. Calculated HOMO (highest occupied molecular orbital) energies reported by Frison and Huyn et al. are included.](image)
Remarkably, for some of these NHCs formal charges have to be added in order to draw a valid Lewis structure of the free ligand, which led to the term meso-ionic carbenes (MICs).\textsuperscript{32,33} The formal negative charge is located partly on the carbene, which is in line with the higher electron-density at that position compared to “classic” NHCs (Figure 3).

The first MIC complex reported was an imidazole-4-ylidene published by Crabtree and co-workers in 2001.\textsuperscript{34} They described the “abnormal” coordination of the NHC, on the 4- instead of the 2-position, in an iridium-hydride complex. Hence, the term abnormal carbene (aNHC) is alternatively used for MICs. This mode of coordination is generally brought about by steric factors or on purpose by synthetically protecting the C2 position of the NHC.

Since the first serendipitous synthesis of a MIC complex, several successors have been developed and 1,2,3-triazol-5-ylidenes (tzNHCs) have advanced to one of the most widely studied and applied classes of “non-classical” NHCs. Triazoles can be easily prepared using Cu(I) catalyzed [3+2] cycloaddition of an alkyne and an azide (CuAAC; Scheme 3)\textsuperscript{35,36} and have been popular research subjects in several research fields such as bioconjugation, material science and medicinal chemistry.\textsuperscript{37} Recently, triazole-based ligands have also found their way into transition metal catalysis, either coordinating to the metal via one of the nitrogen atoms\textsuperscript{38} or as tzNHC (after alkylation of the N3 position).\textsuperscript{33,39,40} The popularity of the latter can be explained by the combination of their specific \(\sigma\)-donor properties, stronger than the most basic classic carbenes yet weaker than imidazole-4-ylidenes (Figure 3),\textsuperscript{1,6} their before-mentioned synthetic accessibility and the endless possibilities to vary the N1 and C4 position through “click” chemistry.\textsuperscript{42–44}

**Scheme 3:** Synthesis of the most common tzNHC precursor, 1,3,4-substituted triazolium salt: Cu(I) catalyzed “click” cycloaddition of an alkyne and azide followed by alkylation of the N3 atom.

The versatility and huge potential of tzNHCs were already predicted in the first report on this highly modular class of MICs published by the group of Albrecht in 2008.\textsuperscript{41} They coordinated the tzNHCs to Pd(II) as well as Ag(I), and used the latter to transfer the carbene to Rh(I), Ir(I) and Ru(II), underlining the versatility of metal insertion.\textsuperscript{41,42} At the start of the research project described in this thesis, however, only few tzNHC complexes were known.\textsuperscript{45–47} Since then, tzNHCs have proven to be useful ligands for catalytic applications. Their metal complexes have been reported as active catalysts for a wide variety of reactions: oxidation, olefin metathesis and
transfer hydrogenation (TH) reactions facilitated by Ru(II),\textsuperscript{45,48-53} Ir(III) catalyzed water oxidations;\textsuperscript{49} Pd catalyzed C-C cross-coupling reactions\textsuperscript{51} and hydroarylation;\textsuperscript{57} and carbene transfer and cyclization reactions by gold complexes.\textsuperscript{58}

1.3 Bi- and Tridentate tzNHC Ligands and their Applications

Bidentate ligands have been often implemented in homogeneous catalysis. First of all because they generally improve the stability of complexes (chelate effect).\textsuperscript{59} More importantly, the combination of different donating atoms in synergy can lead to improved properties of the complex.\textsuperscript{59} The activity of the resulting catalyst may, for example, greatly exceed that of the analogous systems bearing two monodentate ligands.

\textit{Bi- and Tridentate tzNHC Ligands with Heteroatom Donors}

Several chelate donor-functionalized tzNHC complexes have been reported and a selection is depicted in Figure 4.

\textbf{Figure 4:} Structures of selected examples of bidentate tzNHCs bearing heteroatom donors.
These complexes bear at least one anionic or neutral two-electron donor atom (C, N, O, or P) besides the NHC. They can act as bi- or tridentate ligands upon coordination to the metal center.

Gandelman et al. published pincer metal (Pd and Pt) complexes, bearing triazolylidene as central motif flanked by two phosphine donors 1 (Figure 4).60 These complexes were prepared by post modification of the metal complexes, as depicted in Scheme 4. No catalytic applications have been reported for these systems to date.

![Scheme 4: Synthesis of the palladium trazolylidene complex by postmodification published by Gandelman.](image)

The majority of the functionalized tzNHC ligands have a secondary nitrogen donor. Sessler et al. combined two tzNHC ligands with ancillary pyrrole groups. Upon transmetalation of the silver(I) complex with a Ru para-cymene (p-cym) precursor the homodinuclear complex 2 was formed (Figure 4), which was active in the ring-opening metathesis polymerization of norbornene.

Pyridine functionalized tzNHC ruthenium complexes have been described by several groups. Košmrlj and co-workers synthesized several [Ru(η⁶-p-cym)(tzNHC) Cl]+ complexes bearing picolyl and pyridine substituents 3-5 via transmetalation of the corresponding Ag(I) complexes (Figure 4).61 Remarkably, the 1-(2-picolyl)-1,2,3-triazolium salt could not be coordinated following this route. The resulting complexes were applied in oxidation of alcohols with tert-butyl hydroperoxide in water and showed selectivity for benzylic compared to non-benzylic alcohols. The authors argued that this differentiation in combination with the mild conditions and the environmentally benign solvent makes this system superior to similar imidazole-2-ylidene catalysts. The group of Albrecht prepared a series of [Ru(bipy)₂] analogues (bipy = 2,2'-bipyridyl) as photosensitizers for solar energy conversion, including a tzNHC-pyr complex (5c; Figure 4).52 They reported that the tzNHC variant showed promising properties for this application, having the smallest HOMO-LUMO gap (2.41 eV; LUMO = lowest unoccupied molecular orbital) of the synthesized Ru NHC-pyr complexes and a long excited-state lifetime (188 ns).

The group of Albrecht also reported a series of bidentate tzNHC ruthenium p-cym complexes 4-7 with various donor substituents (Figure 4): phenyl anion, carboxylate, and again pyridine (connected via both the N1 and C4 atom of tzNHC).53 The catalysts were applied in alcohol dehydrogenation as well as transfer hydrogenation (TH) and
a significant influence of the donor functionalities was found. Complex 7a with the CC bidentate ligand led to the highest activity for alcohol dehydrogenation, whereas the complex bearing the pyridyl donor (5a) proved the best choice for TH. The authors explained these trends in terms of electron-density on the ruthenium center: neutral weakly donating chelated ligands (e.g. pyridine) lead to a relatively electron-poor metal center that readily binds anions (RO⁻ in this case), leading to good performance in TH, and vice versa. In addition, complexes 5a and 7b have successfully been applied for catalytic water oxidation with cerium ammonium nitrate (CAN) as the sacrificial oxidant.

CC chelating tzNHC complexes 7 and 8 are formed by so-called cyclometalation. Cyclometalation can be promoted by (weak) bases, but spontaneous C-H activation on the N-bound aryl ring occurs with electrophilic metal centers. Stephan et al. reported cyclometalated Ru(II) complexes 8b, derived from the corresponding ruthenium-hydride complex by C-H activation followed by liberation of H₂. The complexes proved to be active catalyst precursors for the hydrogenation of olefins, while leaving other functional groups intact.

Recently, Sarkar et al. reported a series of Cp*-Ir(III) complexes (Cp* = pentamethylcyclopentadienyl) bearing ligands ranging from bipy, pyridyl-triazole, di-triazole to pyridyl-triazolylidene 5b, triazolyl-triazolyldiene 9 (Figure 4) and di-triazolylidene 10b (Figure 5). The complexes were tested for the oxygenation of C-H bonds. The pre-catalyst with unsymmetrical donors, particularly 5b, proved to be the most suitable catalyst for the C-H oxygenation of cyclooctadiene with sacrificial oxidants, outperforming previously reported iridium systems. In this example unsymmetrical tzNHC ligands proved to give the most potent catalysts. However, excellent results have also been obtained with di-tzNHC complexes as described below.

**Bidentate di-NHC Ligands bearing tzNHCs**

Following the success of monodentate NHCs, chelating di-NHCs have become popular ligands in transition metal catalysis. Two strongly bound NHCs lead to enhanced stability of the complex due to the chelate effect as well as an electron-rich metal center. The ligands are good candidates for fine-tuning of catalytic properties by altering the wingtips, backbone and linker. More recently, also di-NHC ligands incorporating tzNHC have been reported, including a few examples of heteroditopic di-NHCs, bearing two different types of NHCs (Figure 5).

Bertrand et al. reported a tzNHC analogue to “bipy”: 1,4-bidentate bis(1,2,3-triazol-5-ylidene) “i-bitz” complex 10c (Figure 5). They isolated the free carbene ligand and a cationic rhodium complex. A similar diisopropylphenyl substituted ligand was
used to prepare half-sandwich Ru(p-cym), 10a, and Ir Cp*, 10b, complexes, that were applied in the transfer hydrogenation of nitrobenzenes. The products formed in the reactions were found to depend on the metal center: anilines for the ruthenium catalysts and azobenzenes when using iridium. The same ligand bearing para-tolyl substituents was used to prepare the heteroleptic Fe(II) complex 10d. The authors postulate that this iron complex, having a relatively long excited-state lifetime, could be the first step to possible future replacement of the expensive Ru(II) photosensitizer by Fe(II).

Another example of a di-carbene is the heteroditopic di-MIC iridium complex 11 that has been applied in water oxidation by Albrecht et al. (Figure 5). In this system a remote abnormal carbene based on pyridine is combined with a tzNHC. More recently, the same group published a homodinuclear version of this complex connected via a propylene linker on the N1. Both complexes were active precatalysts for water oxidation with CAN as sacrificial oxidant, the latter being more active than the monometallic species at low catalyst concentrations.

Series of heteroleptic bis(tridentate) Ru(II) complexes bearing a CNC pincer ditriazolylidene ligand 12 have been developed (Figure 5). These photosensitizers showed excellent properties (e.g. long excited-state lifetime) and have also been immobilized on a TiO₂ surface without loss of charge transfer.

Crudden and co-workers have published complex 13 with two tzNHC wingtips on a 1,3-phenylene core (Figure 5). They synthesized and fully characterized a
dimeric Ag(I) (2:2 Ag:L) complex. Subsequent transmetalation to Rh(I) led to a homodinuclear species with the bidentate ligand acting as a bridge between the two metal centers. The group of Cowie reported homodinuclear rhodium and iridium and heterobimetallic Ir-Rh complexes with the same type of ligand (Figure 5). They recently also prepared heterobimetallic Pd-Rh complexes of this mixed NHC-tzNHC ligand by making use of the different acidities of the two NHCs (Figure 5). Very recent examples of multinuclear NHC complexes concern the phenyl-based di- and tri-tzNHC Pd complexes.

**Cooperative Ligand Systems**

The ligands described so far have been cleverly designed to steer the reactivity of the active metal center. The steric and electronic properties of the ligands determine the performance of the catalysts. The reaction, however, takes place at the metal center and the ligands do not actively participate in the catalytic cycle. Recently, it has become increasingly apparent that this traditional way of considering and utilizing ligands does not realize their full potential. Instead, some ligands can have an active role in the catalytic process, by participating directly in bond activation reactions. This concept, known as metal-ligand cooperativity (MLC), is illustrated by the example depicted in Scheme 5. Here, the benzylic linker of a pincer ligand is deprotonated while the pyridine ring is simultaneously dearomatized. Subsequently, an X-Y bond can be activated over the ligand and metal. The oxidation state of the latter consequently does not change in the process.

![Scheme 5: Schematic representation of the active role of bifunctional ligand via aromatization/dearomatization (right) and hemilability (left).](image)

The so-called “non-innocent” or “bifunctional” ligands in synergy with the metal center have led to unprecedented activities in known catalytic transformations and new catalytic reactions entirely, such as, for instance, coupling of alcohols with amines to form amides with liberation of $\text{H}_2$. In nature, evolution has led to similar cooperative mechanisms: the excellent efficiency and selectivity of enzymes is accredited to the active site being embedded in very specific surroundings. Within homogeneous catalysis, MLC is a relative new yet rapidly expanding field.
The pincer-type ligands containing a central pyridine ring flanked by other ligands, popularized by the group of Milstein, operate via the aromatization/dearomatization mechanism (Scheme 5). Metal complexes bearing these ligands exhibited reactivity in a broad range of useful and environmentally benign reactions. A selection of these, reported by Milstein, include dehydrogenative coupling of primary alcohols to produce esters, the reverse reaction: hydrogenation of esters to alcohols, the direct conversion of alcohols to imines (PNP), amides (PNN) and carboxylic acid salts with liberation of \( H_2 \) and water splitting.

In some of these catalytic reactions, the complexes with the PNN scaffold are excellent catalysts, whereas the PNP analogue is barely active. This has often been attributed to hemilability of the nitrogen donor, i.e. the ability to de- and recoordinate to the metal center (Scheme 5). This feature enables ligands to create vacant coordination sites on the metal, or preorganize or activate the substrate, which may benefit the performance of the catalyst.

The bifunctional approach has also been applied in combination with NHC ligands. One example concerns the bidentate NHC-amine ligands exploited by Morris’ and our group. The complexes 16, bearing such ligands, are active in the reduction of polar bonds (Scheme 6). The hydrogenation was found to proceed via an inner- or outer-sphere mechanism depending on the co-ligand: anionic \( \text{Cp}^* \) ligands lead to the faster outer-sphere mechanism while neutral 1,4-cyclooctadiene (cod) and \( p \)-cymv induce the inner-sphere route.

**Scheme 6:** Mode of action of NHC-amine ligands developed in our group. ML = Ru(\( p \)-cym). Rh- and Ir(cod) catalyze the hydrogenation of polar double bonds via the inner-sphere mechanism, while for ML = Rh- and Ir(Cp\(^5\)) the outer-sphere pathway is operative (box).

To the best of our knowledge, no tzNHC complexes capable of MLC via aromatization/dearomatization have been reported to date. This will be the subject of Chapter 5. More examples of catalytic applications of NHCs are discussed in the next paragraph.
1.4 Catalytic Transformations

As described above, bidentate tzNHC complexes have been applied in many catalytic reactions in the last few years. As these carbene complexes have strong electron-donating properties, they are especially suitable ligands for catalytic transformations that require an electron-rich metal center. The reactions that are studied in this thesis will be discussed below.

Hydrogenation of Unsaturated Bonds

Catalytic hydrogenation of unsaturated bonds is among the most widely studied reactions in chemistry. Reduction of a double or triple bond by the addition of hydrogen is a crucial reaction step in the synthesis of all kinds of chemicals. Traditionally, strong reducing agents like lithium aluminium hydride or sodium borohydride were used stoichiometrically for this transformation, resulting in large amounts of waste. Catalytic hydrogenation, on the other hand, is atom-efficient and generally environmentally benign.

Scheme 7: Two possible catalytic cycles for the hydrogenation: A: hydrogenation of C=C double bond catalyzed by Wilkinson’s catalyst, including the oxidative addition leading to metal hydrides; B: bifunctional mechanism in TH of ketones with isopropanol catalyzed by Noyori’s catalyst.
For catalytic hydrogenation, the splitting of molecular hydrogen or an alternative hydrogen source (\textit{vide infra}) is essential. In homogeneous catalysis this can be achieved by oxidative addition of $\text{H}_2$ to the metal center (Scheme 7, cycle A), which is promoted by electron-rich ligands. Additionally, increased electron-density on the metal gives the hydrogens more hydridic character, due to the back-donation of electrons in the anti-bonding orbital of dihydrogen. Therefore, electron-rich NHC complexes are very suitable candidates to facilitate this reaction. The most well-known homogeneous catalyst for hydrogenation, however, remains Wilkinson’s $[\text{RhCl}(\text{PPh}_3)_3]$ complex.\textsuperscript{94,95} This catalyst is used to depict the general catalytic cycle for hydrogenation in Scheme 7.

Instead of dihydrogen gas, other hydrogen donors can be applied. In this so-called transfer hydrogenation (TH) reaction the donor source delivers hydrogen to the metal center, which in turn transfers it to the substrate. Popular alternative hydrogen donors are isopropanol and formic acid. The former has the advantage that it can serve as the solvent and hydrogen donor at the same time. In the example in Scheme 7 (cycle B), ketones are hydrogenated by Noyori’s ruthenium catalyst using isopropanol as hydrogen source.\textsuperscript{96,97} Here, a bifunctional mechanism is operative: dihydrogen is activated over both the metal and the ligand, as was explained in the previous paragraph. This pathway has led to greatly enhanced reaction rates and has been exploited by many groups over the years. Moreover, the same catalyst system has been expanded very successfully to asymmetric transfer hydrogenation (ATH).\textsuperscript{98} Enantioselective catalysis using NHC complexes will be discussed in more detail in the next paragraph.

Hydrogenation can be used to convert various substrates to useful products. In our group NHC-Pd systems for the transfer semihydrogenation of alkynes with HCOOH/$\text{NEt}_3$ as well as molecular hydrogen have been developed.\textsuperscript{99–102} Semi-hydrogenation of alkynes is a powerful tool to synthesize (Z)-alkenes, which are important building blocks for fine chemicals, such as bioactive molecules, flavors, and natural products.\textsuperscript{103}

Ketones are often used as benchmark substrates for the (transfer) hydrogenation of polar bonds. However, polar double bonds that are not readily reduced by hydrogen gas are of more interest. There is, for example, only a limited amount of catalytic systems known that are able to hydrogenate carboxylic acid derivatives.\textsuperscript{104–107} The relative reactivity in hydrogenation of C=O bonds is depicted in Figure 6.
Due to their thermodynamic stability, esters are a challenging substrate class for hydrogenation. The reduction of esters is formally called hydrogenolysis as the O-R bond is cleaved, leading to two alcohols (Scheme 8). Our group was among the first to convert esters to alcohols under reasonable temperature and pressure (100 °C and 70 bar) using a ruthenium triphosphine catalyst. In the last decade, a lot of progress has been made in catalytic ester hydrogenation. Two Ru di-NHC catalysts capable of facilitating this reaction are highlighted below (Scheme 8).

The first example is a system published recently by the group of Beller (Scheme 8). They screened several NHC ligands in combination with Ru(p-cym) and 30 mol% of base for the hydrogenation of methyl benzoate at 100 °C and 50 bar. The in situ prepared di-NHC catalysts, proved to be superior. Good conversions as well as functional group tolerance were observed for this system. The Ru(II) complex of Song et al. bearing a cooperative CNN ligand (Scheme 8), is active under milder conditions (5.3 bar and 105 °C). This pre-catalyst is slightly more active than the PNN predecessor developed by Milstein, with a TOF of 50 h⁻¹ compared to 8 h⁻¹. Moreover, even the very sterically hindered tert-butyl acetate could be reduced.
Enantioselective catalysis is an important tool within synthetic chemistry because it enables us to selectively produce a desired isomer (enantiomer or diastereomer). The ability to obtain one chiral form of a molecule selectively is essential, especially in the pharmaceutical field, as different stereoisomers often have different biological activity. Besides medicines, applications of chiral compounds include agrochemicals, flavors and materials (e.g. chiral polymers and liquid crystals). The widespread demand for chiral molecules has stimulated research into the development of chiral catalytic systems. This field is dominated by homogeneous catalysts, as these are very selective and can in principle give access to both enantiomers of a product (unlike enzymes).

Considering their popularity in homogeneous catalysis, there are relatively few examples of chiral (di-)NHC metal complexes that have been applied in enantioselective reactions. Efforts to induce chirality with NHCs have been described in some recent reviews. The most convenient way of introducing chirality in these ligands is to introduce chiral substituents on either the backbone or the nitrogen atoms of the NHC. The first chiral NHC complex, of the latter kind was already reported in 1983 by Lappert et al. through the transformation and ring closure of amino acids (Figure 7).

However, research into this kind of complexes showed that, although good results were achieved with some catalysts, the general design for these types of ligands was not effective. Chiral induction was difficult because the chirality was too remotely located with respect to the metal atom, and the dynamic nature of the nitrogen substituents causes the chiral space to be ill-defined, which hinders the transfer of chirality to the substrates.

Bidentate ligands can be used to generate more rigid complexes. Several complexes have been published using chiral di-NHC complexes or an NHC in combination with a hetero-atom donor. Burgess et al. developed the chiral oxazoline-NHC iridium complex 18 for the asymmetric hydrogenation of alkenes (Figure 7).
Furthermore, some chiral di-NHC have proven to be useful in enantioselective catalysis. An example is the \( C_2 \)-symmetric binaphthyl-based Rh(I) complex 19 reported by Shi et al., which will be discussed in more detail in Chapter 6 (Figure 7).

The application of tzNHCs in enantioselective catalysis has barely been explored. In 2009 the first chiral palladium tzNHC complex 20 was obtained via Ag(I) transmetalation (Figure 8).\(^{55}\) Although this catalyst was active in the Suzuki-coupling for the synthesis of biphenyl derivatives, only deborylation of arylboronic acid was observed when it was tested in the asymmetric version of this C-C coupling reaction to produce chiral binaphthyl products.

![Examples of chiral tzNHC complexes.](image)

Aizpura and co-workers reported the axially chiral di-tzNHC complex 21 (Figure 8).\(^{128}\) Although the authors highlighted the potential of this chiral ligand in enantioselective catalysis, no catalytic application has been reported to date.

### 1.5 Outline of the Thesis

In this thesis the design and development of various bidentate di-NHC ligands for organometallic catalysis is described. The coordination to several late-transition metals is studied as well as the application of the resulting complexes in several catalytic transformations. As the employed ligands consist of highly electron-donating species, we focus mainly on hydrogenation reactions, for which such ligands have been shown to be very suitable. At the beginning of this project tzNHC complexes were relatively new ligands and only few applications were known. We aimed to gain fundamental knowledge about the properties of this class of carbenes and di-NHCs in general. By investigating the synthesis, stability and catalytic activity of several late-TM complexes bearing homo- or heteroleptic di-NHC ligands with various substituents, useful information can be obtained on both structure-activity relations and the potential and limits of di-NHCs and tzNHCs concerning complex synthesis and applications in homogeneous catalysis.

The first part of this thesis deals with chelating di-NHC complexes. In Chapter 2 the synthesis of zero- and divalent palladium complexes bearing di-NHC ligands
with various $N$-substituents is described. The resulting low-valent complexes are evaluated in the (transfer) semihydrogenation of alkynes to discover the effect of di-NHC ligands on the performance of the Pd pre-catalysts compared to mono-NHC analogues developed in our group.

Next, heteroditopic di-NHC ligands are introduced. The “click” procedures allows for the convenient synthesis of a series of ligands differing in side-groups, connectivity, chelating ring size and rigidity. In Chapter 3 the coordination of these mixed NHC-tzNHC ligands to Ag(I) Ru(II) and Pd(II) is investigated. The resulting complexes are tested in catalytic hydroarylation of alkynes (Pd) and the reduction of polar double bonds (Ru). Chapter 4 describes the Ir(I) and Rh(I) derivatives of these heteroditopic di-NHC ligands and NHC-triazole analogues thereof. Here, the electron-donating properties of the ligands are assessed further as well as the influence of the parameters mentioned above. The complexes are applied in the catalytic TH of unsaturated bonds with isopropanol as hydrogen donor, in which the effect of the secondary donor as well as the $N$-substituents on the catalytic activity are examined.

The last two chapters feature di-tzNHC complexes. In Chapter 5, the development of lutidine-based pincer complexes (Ag, Pd, Ru) is discussed. Although many cooperative pincer ligands are known and they have shown remarkable reactivity, there were no accounts of such compounds featuring a tzNHC moiety. We expect that this electron-rich donor in combination with the cooperative lutidine core possesses suitable characteristics for efficient Ru-catalyzed hydrogenation of esters.

Chapter 6 describes the design and synthesis of chiral $C_2$-symmetric di-NHC complexes for enantioselective catalysis. Here, the successful binaphthyl backbone is combined with electron-rich 1,2,3-triazolylidene donors to obtain transition metal complexes for enantioselective hydrosilylation of ketones.

### References


Chapter 1

30, 5033–5037.


